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Hereditary Diseases—Causes, Cures, and Problems

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The nature of the biochemical abnormalities in over a hundred inherited diseases of humans is now convincingly established. This impressive achievement has provided numerous practical benefits, amongst which are: 1. accurate methods for the diagnosis of patients with these diseases; 2. identification of symptom-free heterozygous carriers of the defective genes; and 3. procedures for the antenatal detection of a large number of these disorders in fetuses. It is anticipated that equally impressive advances will be made in the future regarding the therapy for patients with these diseases who escape prenatal detection, or in cases when an affected fetus is identified but is carried to term in compliance with the decision of the parents. The current concepts regarding the therapy of heritable metabolic diseases are outlined and potential innovations for future corrective procedures are indicated in this report.

1. Introduction

At the onset of the twentieth century, *Sir Archibald Garrod* began his classic studies on alcaptonuria, a human disease characterized by the gradual darkening of urine when allowed to stand at an alkaline pH, gray to bluish black pigmentation of the patient's tissues, and arthritis which begins at an unusually early age. *Garrod* analyzed the urine of these individuals and clearly demonstrated that they excreted large quantities of homogentisic acid which was present in only trace amounts in normal human urine[1]. He discovered that this disorder occurred in various relatives of the patient. He also showed the same familial penetrance of other human diseases which included: a) albinism which is characterized by a failure of pigment formation; b) pentosuria, in which there is an increased quantity of pentose in the urine; and c) cystinuria, in which patients have an abnormally high level of urinary cystine.

From these observations, *Garrod* derived the remarkable conclusion that these individuals suffered from an inherited deficiency of an enzyme required to catalyze a specific metabolic step in each of these diseases[2]. He correctly predicted the lack of homogentisic acid oxidase in alcaptonuria (Fig. 1). Some 50 years later, the correctness of *Garrod*'s hypothesis was shown by *La Du et al.*[3].

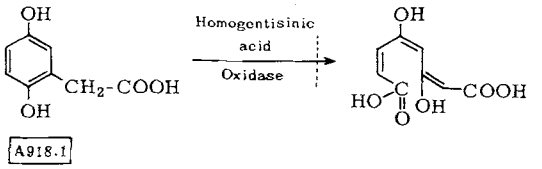

Fig. 1. Homogentisic acid is normally transformed into maleylacetoacetic acid (3,5-dihydroxy-2,4,6-octatrienedioic acid) by the action of homogentisic acid oxidase. The enzyme is lacking in alcaptonuria and no degradation takes place.

Inborn errors of metabolism are directly involved in more than 100 human diseases. These disorders include ab-

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normalities of amino acid metabolism such as phenylketonuria, histidinemia, and hyperprolinemia; derangements of purine metabolism as in orotic aciduria, xanthinuria, and the Lesch-Nyhan syndrome; abnormalities of carbohydrate metabolism such as fructosuria, galactosemia and glycogen storage diseases; derangements of porphyrin metabolism; abnormalities of protein synthesis as in sickle cell disease, agammaglobulinemia and abetalipoproteinemia; and heritable disorders of lipid metabolism such as Gaucher's disease and Tay-Sachs disease.

It is not feasible to discuss or even list all of the known human disorders of metabolism in the present contribution. Excellent standard texts are available in which these disorders and their clinical manifestations are catalogued[4,5]. It is my intention to indicate in this communication how some of the extremely perplexing problems involved in the discovery of the nature of the abnormal enzymology in such diseases have been resolved and to describe some of the practical benefits which resulted from these investigations. It will also be my task to provide a summary of various forms of therapy which seem to be useful at the present time and to suggest avenues of approach which may be helpful in the foreseeable future. I shall deal with lipid storage diseases to a major extent because a number of important, universally applicable concepts were established during investigations of the pathogenesis and management of these disorders.

2. Sphingolipidoses

2.1. General Description

The are now ten distinct disorders of lipid metabolism for which the etiology is convincingly established. The principal clinical manifestations of these diseases are summarized in Table 1. The hallmark of each of these disorders is the accumulation of particular lipids which have a portion of their molecular structure in common. This shared moiety is called ceramide (*N*-acyl sphingosine).

$$CH_3{-}(CH_2)_{12}{-}CH{=}CH{-}CH(OH){-}CH(NHCOR){-}CH_2OH$$

These sphingolipids are primarily localized in membranous elements of the cells throughout the body. One or more molecules of carbohydrate or a phosphorylamine residue is attached to the primary hydroxy group of the sphingosine (Table 2).

Except for Fabry's disease, all of the sphingolipid storage diseases are inherited as autosomal recessive genetic mutations. This means that both parents must be carriers of the defect (heterozygotes) in order to produce an affected child. Carriers are usually entirely free of the signs and symptoms of the disorders. When both parents are carriers, one of four children will have the disease on a statistical basis. Such a child is called a homozygote. Two of their children will be heterozygotes like the parents, and one child will not be involved at all.

Table 1. Salient clinical features of the sphingolipidoses.

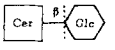
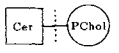
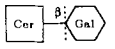
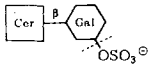
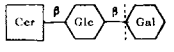
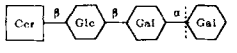
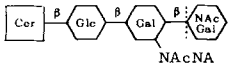
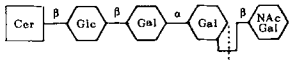
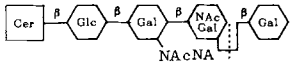
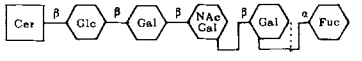
Gaucher's disease	Mental retardation (infantile form only); enlarged liver and spleen; hip and long bone erosion; lipid-laden cells in bone marrow which also stain for carbohydrate; increased serum acid phosphatase; mild anemia; and decreased blood platelets.
Niemann-Pick disease	Generally similar to Gaucher's disease; 30% with cherry-red spot in macula; foam cells in bone marrow which stain for lipid and phosphorus; severe emaciation.
Globoid leukodystrophy (Krabbe's disease)	Mental retardation; almost total absence of myelin; severe scar formation in the brain; multinucleated "globoid bodies" in white matter.
Metachromatic leukodystrophy	Mental retardation; psychological disturbances; decreased nerve conduction time; yellow-brown droplets in nerve fibers when stained with cresyl violet (metachromasia).
Ceramide lactoside lipidosis	Slowly progressing brain damage; large liver and spleen; anemia; decreased number of white blood cells and platelets.
Fabry's disease	Reddish-purple raised rash on abdomen and scrotum; kidney damage; corneal opacities; peripheral nerve pain and electrocardiographic abnormalities.
Tay-Sachs disease	Mental retardation; blindness; cherry-red spot in the retina; enlarged skull; nerve cells distended with "membranous cytoplasmic bodies."
Generalized gangliosidosis	Mental retardation; cherry-red spot in macula (50% of patients); large liver and spleen; foam cells in bone marrow; rarefaction of bones and skeletal deformities.
Fucosidosis	Progressive mental degeneration; weakness and spasticity of muscles; emaciation; thickening of the skin and enlargement of the heart.

The genetic transmission of Fabry's disease is on the X chromosome, and the disorder is therefore carried by the female. Half of the sons born to a female carrier of Fabry's disease will have the full-blown syndrome of Fabry's disease. Fifty percent of her daughters will be carriers, and the other daughters will not be involved. Unlike other sphingolipidoses, the female Fabry heterozygotes may have some of the clinical manifestations of the disease although they usually are much milder than those found in an afflicted male.

The underlying metabolic defect in all of the sphingolipid storage diseases is an attenuation or complete absence of a specific hydrolytic enzyme required for the catabolism of a lipid which occurs in the body as a consequence of the normal turnover of cells and tissues. A second important fact is that the *degree* of enzyme deficiency is similar in all of the organs and cells of the patient. Thirdly, cells obtained from patients with lipid storage disease and grown in tissue culture show the same proportional enzyme deficiency as that which occurs in the organs of the patient from whom the cells were derived. The acquisition of this information now permits the accurate diagnosis of individuals afflicted with any of these lipid storage diseases[6], identification of heterozygous carriers of these disorders[7], and the prenatal detection of fetuses afflicted with any of these diseases[8].

Knowledge of the specific enzymatic defects in the hereditary diseases is mandatory for the development of rational

Table 2. Accumulating sphingolipids and missing enzymes in sphingolipidoses. Cer = ceramide; Glc = glucose; PChol = phosphorylcholine; Gal = galactose; NAcNA = *N*-acetylneuraminic acid; NAcGal = *N*-acetylgalactosamine; Fuc = fucose; NAcGlc = *N*-acetylglucosamine. The position of normal degradation is indicated.

	Disease	Major sphingolipid accumulated		Enzyme defect
1	Gaucher		ceramide glucoside (glucocerebroside)	β-glucosidase
2	Niemann-Pick		sphingomyelin	sphingomyelinase
3	Krabbe		ceramide galactoside (galactocerebroside)	β-galactosidase
4	Methachromatic leukodystophy		ceramide galactose-3-sulfate (sulfatide)	sulfatidase
5	Ceramide lactoside lipidosis		ceramide lactoside	β-galactosidase
6	Fabry		ceramide trihexoside	α-galactosidase
7	Tay-Sachs		ganglioside G_{M2}	hexosaminidase A
8	Tay-Sachs variant		globoside (plus ganglioside G_{M2})	total hexosaminidase
9	Generalized gangliosidosis		ganglioside G_{M1}	β-galactosidase
10	Fucosidosis		H-isoantigen	α-fucosidase

therapeutic measures for the amelioration of these disorders. Wherever feasible, due consideration will be given to potentially useful corrective procedures for the treatment of patients who are not identified prenatally or where the parents have elected to continue the pregnancy despite the identification of an affected fetus.

2.2. Gaucher's Disease

Gaucher's disease is the first sphingolipodystrophy in which the nature of the metabolic derangement was conclusively demonstrated. A number of important concepts were established in the course of studies on Gaucher's disease which have been applied to all other lipid storage diseases. A brief description of historical developments will be presented since the discovery of the etiology of many other inherited disorders followed these precepts.

The lipid which accumulates in the tissues of patients with Gaucher's disease is glucocerebroside (Table 2, row 1). The hexose portion of glucocerebroside is to be contrasted with that in galactocerebroside, the predominant glycolipid of the myelin sheath of nerves (Table 2, row 3). This difference gave rise to several hypotheses regarding the etiology of Gaucher's disease which included:

1) an abnormality of carbohydrate (galactose) metabolism;

2) an overproduction of glucocerebroside in tissues; and

3) a deficiency of a catabolic enzyme required for the degradation of glucocerebroside.

The first two hypotheses were shown to be untenable in studies by *Thannhauser*[9] and by *Trans* and *Brady*[10], respectively. The nature of the metabolic defect in Gaucher's disease was established by the following series of experiments. Glucocerebroside was synthesized with ^{14}C in the D-glucose portion of the molecule[11]. With this labeled material as substrate, an enzyme was demonstrated in all of the tissues of the body which catalyzes the hydrolysis of glucocerebroside.

$$\text{Glucocerebroside} + H_2O \xrightarrow{\text{glucocerebrosidase}} \text{glucose} + \text{ceramide}$$

This enzyme was found in high activity in the spleen and was partially purified from this tissue. Optimal incubation conditions, kinetics, and products of the reaction were determined. The activity of the glucocerebrosidase was then measured in samples of human spleen tissue obtained at operation from a control series of patients and from patients with Gaucher's disease. The mean level of glucocerebrosidase activity in the specimens from patients with the "adult" form Gaucher's disease was 15% of that found in the controls[12–15]. Specimens of spleen tissue obtained from patients with the more rapidly progressing "infantile" form have extremely little if any glucocerebrosidase activity.

The glucocerebroside which accumulates in the spleen, liver, and bone marrow is derived from lipids in the membranes of senescent red and white blood cells. The principal neutral glycolipid of leukocytes is ceramide lactoside (Table 2, row 5). A second important source of glucocerebroside in peripheral tissues is globoside (Table 2, row 8), the principal glycolipid of red blood cells. These substances are degraded enzymatically in a stepwise fashion to cer-

amide-glucoside (glucocerebroside) which accumulates in patients with Gaucher's disease because of the deficiency of the requisite β-glucosidase. Glucocerebroside also accumulates in the nerve cells of patients with the infantile form of Gaucher's disease and probably arises from the turnover of gangliosides (Table 2, rows 7 and 9).

The diagnosis of Gaucher's disease can be established by measuring glucocerebrosidase activity with ^{14}C-labeled glucocerebroside in samples of tissues obtained by biopsy or in leukocytes obtained from small quantities of venous blood[16]. Leukocyte preparations and cultured skin fibroblasts are also useful for the detection of Gaucher heterozygotes[7]. The fluorogenic artificial substrate 4-methylumbelliferyl β-D-glucoside (Fig. 2) has recently been used for the detection of homozygotes and heterozygotes[17,18].

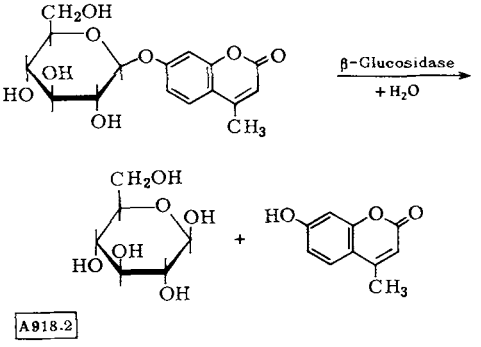


Fig. 2. 4-Methylumbelliferyl β-D-glucopyranoside, an artificial substrate for measuring β-glucosidase activity. The resulting 4-methylumbelliferone fluoresces.

Diagnostic enzyme assays are of maximum utility when applied to the monitoring of pregnancies at risk for heritable metabolic diseases. At the present time the procedure of choice is the determination of activity in extracts of cultured fetal cells obtained by amniocentesis (Fig. 3). This technique may be used for the identification of fetuses which are heterozygous[7] and homozygous[19] for Gaucher's disease. It is anticipated that eventually artificial substrates will become useful for prenatal diagnosis of Gaucher's disease.

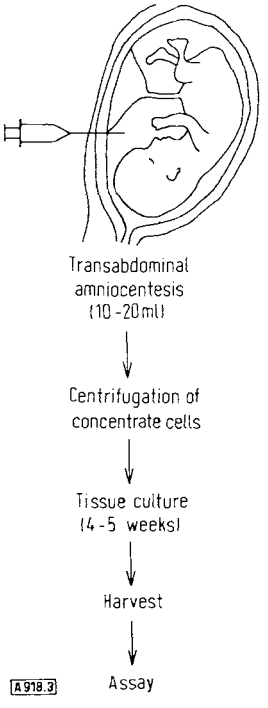


Fig. 3. Prenatal detection of genetic abnormalities.

2.3. Niemann-Pick Disease

Klenk was the first to identify sphingomyelin as the accumulating lipid in patients with Niemann-Pick disease[20]. Once again, the deficiency of a catabolic enzyme was shown by metabolic studies performed with sphingomyelin labeled in the choline portion of the molecule[21]. The mean level of sphingomyelinase activity in liver preparations from Niemann-Pick patients was 7% of that of control series[22]. Erythrocyte stroma is again a likely source of the accumulating sphingomyelin, since, next to lecithin and phosphatidyl ethanolamine, it is the predominant phospholipid of the red cell membrane. Sphingomyelin is also a major lipid constituent of all subcellular elements and the plasma membrane of cells; therefore, it seems likely that sphingomyelin could arise as a consequence of turnover of cellular elements in most if not all tissues.

The diagnosis of Niemann-Pick disease may be confirmed by determining sphingomyelinase activity in tissue biopsies, sonicated leukocytes[16], or extracts of cultured skin fibroblasts[23]. An artificial chromogenic substrate, 2-*N*-acylamido-4-nitrophenylphosphorylcholine, for measuring sphingomyelinase activity has recently been proposed[24] (Fig. 4). It must be determined whether this compound will provide an accurate indication of sphingomyelinase activity in various cells and tissues. Satisfactory assay procedures have recently been developed for the detection of heterozygous carriers of Niemann-Pick disease[6,7]. The prenatal diagnosis of fetuses afflicted with Niemann-Pick disease is now a proven procedure[25]

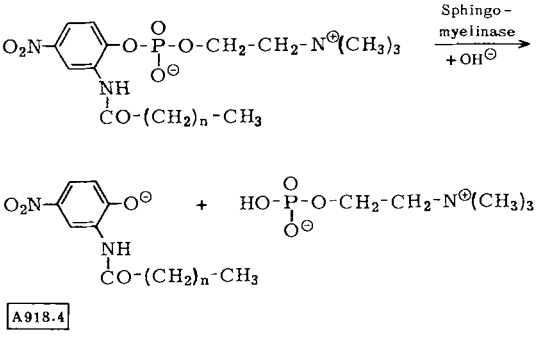


Fig. 4. 2-*N*-Acylamido-4-nitrophenylphosphorylcholine, an artificial substrate for measuring sphingomyelinase activity. The resulting 2-*N*-acylamido-4-nitrophenoxide ion is yellowish orange.

2.4. Globoid Leukodystrophy: Krabbe's Disease

The metabolic defect in patients with this disorder is a deficiency of a β-galactosidase which catalyzes the hydrolysis of galactocerebroside (Table 2, row 3)[26]. The accu-

mulating galactocerebroside is presumed to arise from the turnover and restructuring of myelin during the development of the nervous system. Patients with this disorder may be diagnosed by determining galactocerebrosidase activity in circulating leukocytes and cultured skin fibroblasts[27]. Heterozygotes are best demonstrated through similar assays with serum samples. The prenatal detection of a fetus afflicted with Krabbe's disease has recently been reported[28].

2.5. Metachromatic Leukodystrophy (MLD)

Sulfatide (Table 2, row 4) accumulates in various tissues of patients with this disease. The biochemical defect in MLD is a deficiency of the enzyme which catalyzes the hydrolysis of sulfatide[29, 30]. The enzyme is generally designated as arylsulfatase A because its catalytic activity is frequently determined using arylsulfate esters as substrate (Fig. 5). Patients and heterozygous carriers may be detected by determining arylsulfatase A activity in circulating leukocytes[31–33] and extracts of cultured skin fibroblasts[34]. It is anticipated that this assay procedure will be useful for the prenatal detection of fetuses with MLD.

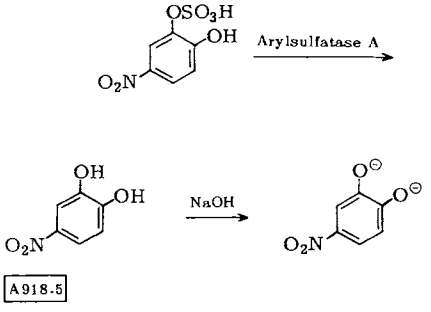


Fig. 5. 2-Hydroxy-5-nitrophenyl sulfate, an artificial substrate for measuring arylsulfatase activity. The sulfate and 4-nitropyrocatechol are yellow, the anion (pH = 11—12) is red.

2.6. Ceramide Lactoside Lipidoses

A patient has recently been described in which ceramide lactoside (Table 2, row 5) is the principal accumulating lipid. The metabolic defect is a deficiency of the β-galactosi dase which catalyzes the hydrolytic cleavage of the molecule of galactose from ceramide lactoside[35]. For the accurate identification of homozygotes and heterozygotes[36] the use of galactose-labeled ceramide lactoside[37] is mandatory at the present time.

2.7. Fabry's Disease

This condition is a lipid storage disease in which ceramide trihexoside (Table 2, row 6) accumulates in various tissues of these patients, especially in the kidney. The enzymatic defect is a deficiency of ceramide trihexoside-α-galactosidase[38]. Highly purified enzyme has been obtained from small intestinal tissue[39]. The principal source of accumulating ceramide trihexoside is globoside (Table 2, row 8) from senescent erythrocytes.

Enzymatic assay with biopsy specimens of small intestinal mucosa is a satisfactory procedure for diagnosing patients and heterozygotes[38]. A more convenient procedure has recently been developed in which artificial chromogenic or fluorogenic α-galactopyranosides are used as substrates[40]. Refined methods have been developed for measuring glycolipids in urine sediment and this procedure is a useful adjunct both for identifying patients with Fabry's disease as well as other sphingolipidoses[41]. The prenatal detection of Fabry's disease is now an established procedure[42].

2.8. Tay-Sachs Disease

This disease occurs in approximately one in 6000 births in infants of Ashkenazic Jewish parentage. The disorder has been reported in many other groups, but the frequency in non-Jews is on the order of one-hundredth of that in the Jewish race. Histological examination of the brain reveals swollen neuronal cells in various stages of degeneration, and many of them contain concentrically-layered electron-dense "membranous cytoplasmic bodies" (MCB's) (Fig. 6). The MCB's are comprised of protein, cholesterol, phospholipid, and Tay-Sachs ganglioside (G_{M2}) (Table 2, row 7), the pathognomonic substance which accumulates in the brain of patients with this disorder. Another sphingolipid,

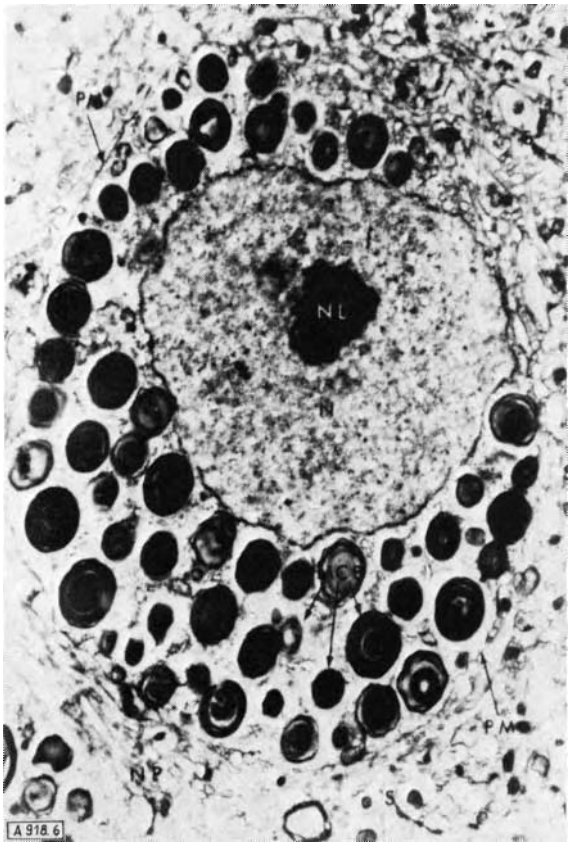


Fig. 6. Membranous cytoplasmic bodies (MCB) in a nerve cell from a patient with Tay-Sachs disease [43]. N = nucleus; NP = nucleolus; PL = plasma membrane.

asialo-Tay-Sachs ganglioside[*] (ceramide-glucose-galactose-*N*-acetylgalactosamine) is also increased in the brain in these infants, but to only one-fifth of the extent of G_{M2}. The accumulating lipids are primarily confined to the central nervous system with the notable exception that the neurons of the intestine are frequently involved.

The discovery of the specific enzymatic defect in Tay-Sachs disease was hindered by the difficulties encountered in preparing appropriately labeled G_{M2} for metabolic studies. This molecule has yet to be synthesized by organic chemists. In time, G_{M2} labeled with ^3H in the *N*-acetylneuraminic acid moiety was prepared by a combination of biosynthesis *in vivo* and selective enzymatic degradation of the mixed radioactive gangliosides obtained in this fashion[44]. G_{M2} labeled with ^{14}C in the *N*-acetylgalactosaminyl moiety was also prepared through enzymatic synthesis *in vitro*[45]. Using these specifically labeled substances, it was shown that the catabolism of G_{M2} can be initiated either by the cleavage of the molecule of *N*-acetylneuraminic acid[46] or the molecule of *N*-acetylgalactosamine[47]. G_{M2}-neuraminidase activity is normal in tissues obtained from patients with Tay-Sachs disease[48] whereas there is a drastic attenuation of G_{M2}-hexosaminidase[48-50]. These findings support the concept that the hexosaminidase isozyme A which was shown by artificial substrates to be lacking in patients with Tay-Sachs disease[51] is involved in the catabolism of G_{M2}. The complete elucidation of the pathogenesis of Tay-Sachs disease is complicated by the fact that these two pathways exist for the degradation of G_{M2} in normal human tissues and that only one of them, the hexosaminidase route, is disturbed in patients with Tay-Sachs disease[49, 50, 52].

In the tissues of patients with a second or "O variant" form of Tay-Sachs disease there is a decrease of total hexosaminidase activity[53]. This disorder is confined mainly to patients of non-Jewish extraction. In addition to the accumulation of G_{M2} in the brains of these patients, globoside accumulates in peripheral organs (Table 2, row 8).

There is also a third category of patients with Tay-Sachs disease called the "AB-variant" in which hexosaminidase isozymes A and B are both *present* when assayed with artificial substrates; however, the catabolism of G_{M2} is impaired in these patients[53]. Nevertheless, with the exception of the "AB-variant," the diagnosis of Tay-Sachs homozygotes and heterozygotes is readily accomplished through hexosaminidase assays using serum samples[54]. The prenatal detection of fetuses afflicted with Tay-Sachs disease has been reported[55, 56].

2.9. Generalized (G_{M1}) Gangliosidosis

The principal substance which accumulates in the nervous system of patients with this disorder is ganglioside G_{M1} (Table 2, row 9). This condition is therefore frequently referred to as G_{M1}-gangliosidosis. Along with some accumulation of G_{M1}, a keratan sulfate-like mucopolysaccharide is increased in the peripheral tissues of patients with this disorder. The disease is caused by a deficiency of G_{M1}-ganglioside-β-galactosidase which catalyzes the hydrolysis of the terminal molecule of galactose from monosialyltetrahexosyl ganglioside[57]. Patients with this disorder have a decrease of total tissue β-galactosidase activity as measured with artificial substrates.

Due to this very drastic lowering of galactosidase, it might be anticipated that other substances having a terminal molecule of galactose such as galactocerebroside (Table 2, row 3) or ceramide lactoside (Table 2, row 5) might accumulate along with G_{M1}. This has not been observed; in fact, the activity of the enzymes which catalyze the hydrolysis of galactocerebroside and ceramide lactoside are actually increased 4- to 5-fold in the tissue of these patients[58]. Nonetheless, artificial galactopyranoside substrates are very useful for the diagnosis of homozygotes, for identifying heterozygotes[59], and for the prenatal detection of G_{M1}-gangliosidosis[60]. The accumulating G_{M1} may arise from the turnover of plasma membrane components of various cells since gangliosides are highly concentrated in these structures[61, 62].

2.10. Fucosidosis

A discussion of lipid storage diseases should include some recent observations on a small group of patients with a disorder called fucosidosis[63]. The enzymatic defect is a complete deficiency of α-L-fucosidase in the tissues of these patients[64]. The natural substrate(s) of this enzyme is not well established; however, it is well known that intestinal tissue, red blood cells, and certain other tissues contain fucoglycolipids with H, Le^a, and Le^b isoantigenic activity[65]. In accordance with the anticipated pathophysiology of this disorder, a very large increase in pentahexosylfucoglycolipid has been observed in liver tissue obtained from a patient with fucosidosis[66]. It is presumed that the specific metabolic defect in this disease will soon be conclusively demonstrated and that it will be a deficiency of a fucosidase involved in the catabolism of fucolipids (Table 2, row 10).

3. Treatment

3.1. Gaucher's Disease

A number of potential forms of therapy have been envisaged for the correction of inherited metabolic diseases[67, 68], but so far only a modest amount of direct experimentation has been carried out. Patients with Gaucher's disease often require supportive therapy such as vitamins, supplemental iron or liver extract for the anemia, and splenectomy because of the development of hemorrhagic tendencies. Aside from these palliative measures, the principal concept for the therapy of Gaucher's disease is the hope of devising a procedure for restoring enzyme activity in the tissues of these patients (Table 3). Since spleen has high glucocerebrosidase activity, transplantation of this organ has long been considered as a therapeutic procedure for these patients[67]. Techniques have been developed for this

[*] *N* or *O*-Acylated neuraminic acids are also called sialic acids.

operation and it has recently been performed on a patient with Gaucher's disease[69]. The total plasma lipid hexose level decreased for a short period of time post-operatively in this patient; however, there was only a slight diminution in circulating glucocerebroside. The patient expired three months after the operation. It must be concluded from this important study that spleen transplantation is still a very hazardous undertaking and the efficacy of the procedure for the treatment of patients with Gaucher's disease is very much in doubt.

Table 3. Therapeutic possibilities.

1. Enzyme replacement
   1.1. Organ transplantation
2. Parenteral administration of purified enzymes
   2.1. Animal sources
   2.2. Human preparations
   2.3. Encapsulated enzyme in biodegradable microspherules
3. Percolation of blood over stably bound enzyme
4. Administration of DNA
   4.1. Transducing viruses
5. Anti-enzyme antibodies
6. Hybridization and replacement of patient's cells
7. Administration of metabolic cooperativity material

The therapeutic approach which is receiving the most serious consideration at the present time is the possibility of replacing the missing enzyme by parenteral administration of purified glucocerebrosidase. The enzyme has been partially purified from human spleen[11], and a more highly enriched preparation has been obtained from beef spleen tissue[70]. Glucocerebrosidase has recently been obtained in a high degree of purity from human placental tissue[71]. We prefer to use enzyme isolated from human sources because of the expectation that such preparations will be the least likely to cause an untoward immunological reaction when injected into patients. Considerable experimental evidence indicates that exogenously administered enzymes will be taken up by the cells of the reticuloendothelial system[72], a highly desirable situation for attempting to treat patients with Gaucher's disease. One wonders if the concentration of exogenous enzyme would be increased in these cells if the enzyme were encapsulated in a biodegradable "liposome"[73]. The rationale of parenteral enzyme therapy receives some support from investigations in which α-glucosidase was administered to mice and to patients with glycogen storage disease. Liver glycogen fell in the experimental animals[74] and in two patients with glycogenosis[75, 76].

However, a negative report of an essentially similar therapeutic attempt has appeared[77]. All of the preceding studies were performed with very crude glucosidase preparations obtained from the fungus *Aspergillus niger* and there was a wide variation in the frequency and quantity of enzyme injected. It is therefore virtually impossible to draw relevant conclusions regarding the effectiveness of this therapeutic approach from these published reports.

Enzyme replacement procedures may eventually become useful for reducing the level of the accumulated lipid in peripheral organs and tissues, but it seems doubtful whether a sufficient quantity of parenterally administered enzyme would cross the blood-brain barrier to be an effective form of treatment for patients with central nervous system difficulties. Alternative procedures have been contemplated for increasing the level of enzymatic activity in the brain and all of the current concepts seem potentially quite dangerous. One technique which may be examined for its clinical usefulness is the temperary opening of the blood-brain barrier by the intracarotid injection of a hypertonic solution of urea or other solute[78]. Much refinement and additional experimentation must be carried out prior to clinical attempts with this procedure since in its present form it often causes a variable degree of paralysis in experimental animals.

Another potential form of therapy which may still be remote, but has recently been brought a little bit closer to the experimental stage is the long-sought procedure for transducing human cells with a virus carrying the genetic message for a missing enzyme—genetic engineering[79].

Two major obstacles must be overcome before this approach can be considered appropriate for human trial. The first of these is the enormous number of infectious virus particles which must be administered in order to obtain a stably transduced cell. At the present time, this ratio ranges from 1000 to 10000 virus particles per cell. The viremia and viral encephalitis which must necessarily accompany such a therapeutic attempt are clearly unsupportable. It may be hoped that procedures will be discovered which will drastically reduce the presently required high multiplicity of infectious particles; for example, development of a technique similar to the use of heat-inactivated Sendai virus which has been so helpful for preparing hybridized cells.

Secondly, the viruses presently available for cell transduction are primarily of the λ-phage group which normally infect and extract DNA from *E. coli*. As far as known, this microorganism does not contain any of the sphingolipid hydrolases, and therefore another source of the replacement cistron must be sought. One conceivable source may be *H. ciferii*, a yeast which is rich in sphingolipids. It is not known whether an appropriate virus can be obtained for transduction experiments with such cells.

An additional concept regarding potential forms of therapy of lipid storage diseases should be borne in mind. It has been shown in a number of instances that anti-enzyme antibodies cause an enhancement of enzymatic activity under certain conditions[80–83]. This is potentially an important finding since the first two of these reports deal with the activation of mutant enzymes obtained from *E. coli* which are catalytically inactive in the absence of the appropriate antibody. When antibody was added to the assay mixtures, the level of enzymatic activity approached that of the wild type nonmutated enzyme. The potential importance of this observation is underscored by the fact that there are proteins in the tissues of patients with several genetic diseases which cross-react with antibodies directed towards the normal human enzymes[84, 85]. It is therefore conceivable that mutated human enzymes with low catalytic efficiency might be activated through administration of an appropriate antibody. This novel concept also requires extensive additional experimentation

before attempting to exploit this phenomenon for the treatment of human diseases, since the possibility of induced amyloidosis[86] must be rigidly excluded.

3.2. Niemann-Pick Disease

Again one must consider the possibility of exogenous administration of the requisite enzyme. Sufficient quantities of purified human sphingomyelinase have not been available for therapeutic trials. Perhaps in time it will be possible to consider liver transplantation for the amelioration of this disease. Alternatively, it may be worthwhile exploring the possibility of administering sphingomyelinase prepared from other than human sources, such as beef liver or even a suitably purified enzyme from bacteria[87]. However, an additional precaution must always be kept in mind when considering enzyme replacement therapy for Niemann-Pick disease, namely the ubiquitousness of sphingomyelin. It is conceivable that the parenteral administration of sphingomyelinase might cause hemolysis of erythrocytes and general cellular disintegration with serious sequelae. In order to preclude such untoward effects, sphingomyelinase may well be an ideal enzyme for administration in biodegradable microspherules.

3.3. Krabbe's Disease

Enzyme replacement therapy is high on the list of possible restorative procedures although again the possibly limited access of a parenterally administered enzyme to the nervous system may preclude its effectiveness. The investigation of therapeutically distinct approaches in this disease has one particular advantage which is the well documented observation that certain strains of dogs are affected with a form of globoid cell leukodystrophy which resembles the disorder in humans in many respects[88]. An unusual opportunity is thereby afforded for examining potential remedial procedures with this animal model. The principal limitation at present is the lack of sufficient quantities of highly purified galactocerebrosidase for these investigations. Hopefully this restriction will soon be surmounted.

3.4. Metachromatic Leukodystrophy (MLD)

There have been two noteworthy attempts of enzyme replacement therapy for MLD. The first was carried out by *Austin* in 1967, when he infused a relatively crude preparation of human urinary arylsulfatase intrathecally into a patient with MLD[89]. The patient had a severe pyrogenic reaction and there was no evidence of clinical improvement. In another study, a partially purified preparation of beef brain arylsulfatase A was administered intravenously and intrathecally[90]. The patient became febrile and again no clinical improvement was observed. Enzymatic activity was detected in the liver following intravenous infusion, but no enzyme was found in the brain.

These studies are very discouraging from the standpoint of enzyme replacement therapy. However, a glimmer of encouragement may be derived from the recent report that the quantity of sulfatide in cultured fibroblasts derived from a patient with MLD decreased when crude urinary arylsulfatase A was added to the culture medium[91]. These studies re-emphasize the need for devising new concepts and approaches to try to overcome the enzymatic deficiency in the nervous system.

3.5. Fabry's Disease

The administration of moderate quantities of diphenylhydantoin often relieves the pain of the peripheral neuralgia which rather commonly occurs in teenage patients with Fabry's diesease[92]. We have obtained homogeneous preparations of ceramide trihexosidase from human urine and placenta[93]. Replacement trials with these enzyme preparations will be undertaken soon.

Another approach which has been suggested for the treatment of patients with Fabry's disease is the possibility of kidney transplantation[94]. An informative study along these lines was carried out by *Phillippart*[95] who found a temporary decrease in the level of plasma ceramide trihexoside postoperatively. However, there was a gradual return of ceramide trihexoside towards the preoperative level in the plasma after the kidney transplants in spite of apparently satisfactory function of the grafted kidneys.

Another procedure which has been investigated for the amelioration of Fabry's disease is the infusion of fresh normal human plasma into these patients. It has been claimed that the circulating ceramide trihexoside level decreased as a result of this procedure and that plasma ceramide trihexosidase activity in the patients increased to a surprisingly high value[96]. This report has caused much concern and more than a little controversy since most laboratories[97, 98], including the author's, have been unable to demonstrate the hydrolysis of galactose-labeled ceramide trihexoside catalyzed by plasma preparations. Therefore, I feel it is necessary to withhold judgment at this time regarding the effectiveness of plasma infusion for the treatment of Fabry's disease.

The possible use of polymer-bound enzymes deserves consideration at this point. We have very recently covalently coupled ceramide trihexosidase to a polyacrylamide matrix[99]. The rationale for this approach is the desire to pass whole blood (or plasma) over a column of the stabilized enzyme in the hope that the elevated level of circulating ceramide trihexoside in patients with Fabry's disease[100] will be decreased by this procedure. It is anticipated that such a lowering of plasma ceramide trihexoside will induce the egress of the accumulated glycolipid from the tissues of these patients. The major obstacle of this form of therapy is the complicated procedure involved in providing an absolutely sterile exteriorized arterio-venous shunt. The difficulties are comparable to those of hemodialysis, a procedure often required for treating patients with Fabry's disease. However, an additional constraint on this procedure for the treatment of Fabry patients is the fact that the maximal catalytic activity of the enzyme occurs at pH 5.0; many predictable problems will be encountered if the pH of the blood or plasma is lowered to this value.

3.6. Tay-Sachs Disease

A considerable amount of investigative effort is currently directed towards enzyme replacement therapy for patients with the "B-variant" form of Tay-Sachs disease. The missing enzyme, hexosaminidase A, has been purified to homogeneity from human placenta and urine[101]. An investigation has been carried out on the distribution of the enzyme after intravenous infusion in a patient with Tay-Sachs disease. Enzymatic activity disappears very rapidly from the blood stream with the kinetic course indicated by the following equation[102]:

$$\text{Hexosaminidase activity} = e^{e^{(-.0083t + 1.84)}}$$

Some hexosaminidase A activity appears in the liver after infusion; however, only a very small amount of enzyme entered the brain. Obviously, much additional investigation must be carried out along these lines.

Since there is considerable hexosaminidase A and B activity in serum, as measured with artificial substrates, a number of therapeutic trials may be expected utilizing fresh human plasma as a source of hexosaminidase. There are several major drawbacks to this approach among which are the large quantities of plasma which would have to be infused; however, this limitation might be circumvented to a degree by enzyme concentration procedures.

A second, more important drawback, is the complete lack of evidence that circulating plasma hexosaminidase catalyzes the hydrolysis of G_{M2}, the accumulating lipid. Thirdly, there is the ever-present doubt whether a sufficient quantity of enzyme can enter the brain from the blood. Other than altering the permeability of the blood-brain barrier[78] which is at best a potentially hazardous procedure, or genetic engineering[79] which is currently viewed with extreme skepticism, the most logical approach appears to be to try to devise a procedure to chemically modify hexosaminidase so that it will pass through the blood-brain barrier while retaining activity towards the natural substrate. I suggest that an attempt be made to chemically modify the enzyme by the covalent attachment of medium chain length aliphatic amino alcohols to the protein. I predict that this procedure will be a principal avenue of investigation for the treatment of Tay-Sachs disease in the near future.

3.7. G_{M1}-Gangliosidosis

Concepts relevant to the treatment of patients with this disorder generally follow those described for Tay-Sachs disease and the other lipid storage diseases. The β-galactosidase involved has been obtained in a purified form from mammalian liver tissue[103]. One important advantage of this enzyme preparation is its high activity toward G_{M1}, the natural lipid substrate. However, the precautions discussed in the section on Niemann-Pick disease regarding enzyme infusion may well apply when considering replacement trials for G_{M1}-gangliosidosis since gangliosides are important components on the surfaces of many cells.

3.8. Additional Measures

A potential corrective procedure which is receiving considerable attention at the present time is the possibility of hybridizing some of the patient's cells with other human cells which contain the cistron for the defective enzyme. A very interesting experiment along these lines was reported by *Nadler et al.* who hybridized human cells from patients with galactosemia[104]. These individuals are deficient in the enzyme galactose-1-phosphate uridyl transferase:

Galactose-1-phosphate + uridinediphosphate glucose $\xrightarrow{\text{transferase}}$ uridinediphosphate galactose + glucose-1-phosphate

The hybrid cells contained catalytically active enzyme. These data suggest that the enzymatic defects in the parent cell lines were due to different point mutations in the genetic code and that interallelic complementation (correction) had occurred in the hybrid cells. These experiments open the possibility of reimplanting cells in patients after hybridization has been carried out in tissue culture.

Two very important precautions must be constantly kept in mind when contemplating the therapy of human disease by this procedure. The first is the danger of producing an antigenically incompatible cell which would be rapidly rejected by the recipient. Perhaps this potential difficulty can be circumvented by proper selection and cloning of hybridized cells whose complement of antigens is compatible with the recipient. Secondly, and perhaps potentially even more hazardous, is the fact that spontaneous malignant transformation is not an infrequent phenomenon in cultured cells. It is especially likely to occur if repeated passages of the cells are carried out. Tests to exclude this untoward reaction are very difficult since they would have to be performed in experimental animals. The reliability of data obtained in this fashion for extrapolation to humans would certainly be questionable.

Some very recent reports contain data which permit my closing this dissertation on a cautious note of optimism. In 1966, *Suback-Sharpe, Bürk*, and *Pitts* reported that baby hamster kidney cells which were deficient in inosinic acid pyrophosphorylase (Fig. 7) showed evidence of correction

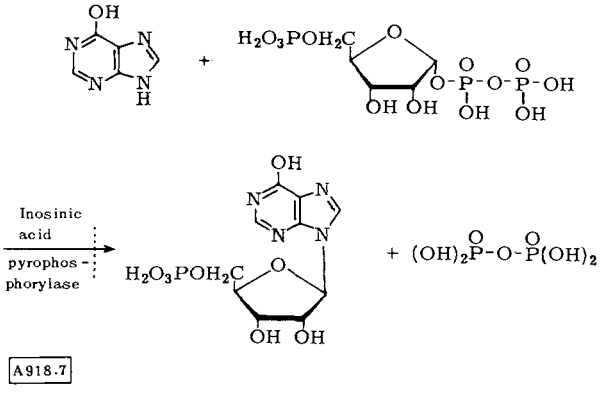


Fig. 7. Hypoxanthine and α-5-phospho-6-ribosyl 1-pyrophosphate are normally transformed into inosinic acid and pyrophosphate by the action of inosinic acid pyrophosphorylase.

of the metabolic defect if they were grown in the presence of normal cells or cells deficient in a different enzyme[105]. This observation has been amply confirmed and the restoration phenomenon is called "metabolic cooperativity". It appears that a "factor" passes between the cells and the agent responsible for such correction in patients with mucopolysaccharidoses appears to be a protein[106]. Similar corrective factors have been found in blood plasma and urine. The latter observations prompted *Di Ferrante et al.* to undertake therapeutic trials of plasma infusion in patients with mucopolysaccharide accumulation[107]. The investigators were encouraged by their results and the experiments were extended to an examination of the effect of transfusing leukocytes in a patient with a similar disorder[108]. The patient was said to have benefited by this procedure and the results were considered to be superior to those obtained with plasma infusion.

These reports have prompted a spate of clinical investigations along this line and both positive[109] and negative[110] clinical responses have been obtained. It is my feeling that this technique clearly warrants extensive investigation at this time. It is certain that leukocyte transfusion will be tried in other metabolic diseases, for example in the sphingolipidoses. The reasonableness of this approach is indicated by the fact that leukocytes contain glucocerebrosidase[16], galactocerebrosidase[111], and sphingomyelinase[16] activity. Caution and restraint are required on the part of the investigator lest he carry this concept too far. For example, implantation of bone marrow cells has been suggested as a possible approach for providing a stable, constant source of cells for patients with immunological deficiencies. It was concluded in a recent survey that this form of therapy is a very hazardous procedure at this time[112].

4. Conclusions

I have attempted to provide a précis of current concepts for the therapy of inherited diseases and to indicate points of departure for future explorations. Circumspection, imagination, and caution are required in order to mount effective therapeutic regimes for the treatment of these disorders. A number of potential approaches are described and evaluated in this review. Some of these possibilities are worthy of exploration at this time; others must await further innovation and improvement. High on the list of potentially effective procedures are replacement trials with purified enzymes and the administration of metabolic cooperativity factors. These approaches appear likely to be beneficial for a limited number of conditions. Other, more generally useful, forms of therapy must be developed for the amelioration of the majority of heritable human diseases.

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The Loose Connection between Electron Configuration and the Chemical Behavior of the Heavy Elements (Transuranics)[**]

By Christian Klixbüll Jørgensen[*]

There is no straightforward relation betwee n the ground electron configuration of the neutral atom and the chemistry of a given element. n particular, the choice of oxidation state depends on the comparison between consecutive onization energies of the gaseous ions and the hydration energy or Madelung energy w] ich by preference stabilizes increased oxidation numbers. Special ligands, such as oxide, may introduce unexpectedly high oxidation numbers. The baricenters of electron configurations are discussed with vanadium and thorium as specific examples. The chemistry of the elements with $Z=101$, 102, 103, 104, 105, and 112 (of which some thousand atoms have been reported) and the (yet unknown) elements with $Z=108$, 109, 114, 126, 164, and 184 is discussed.

Originally, *Mendeleev* arranged the elements in periods of the same length, each period containing seven elements, and after the discovery of the noble gases, eight elements. This proved to be unsatisfactory for various reasons; not only do three "triad elements" sometimes replace one noble gas, but also the oxidation numbers of copper(II) and gold(III) are higher than the number of the column in the Periodic Table, thus giving an impression of transitional "tetrads". *Rydberg* was the first, in 1906, to suggest increasingly long periods of 2, 2, 8, 8, 18, 18, 32, 32, 50, ... elements, these numbers being twice the squares of integers[1]. This conjecture turned out to be right with exception of the two "elements" nebulium and coronium, which ought to form the second period; and the spectral lines of nebulium and coronium corresponded exactly with those of highly ionized oxygen and iron, respectively. If *Rydberg* was right, fourteen rare earths follow lanthanum, all being predominantly trivalent, whereas hafnium is quadrivalent and tantalum mainly quinquivalent. This proved to be in complete agreement with subsequent discoveries. Actually, all the lanthanoids had already been separated by painstaking fractional crystallization[2]; the one exception being $Z=61$, which has only radioactive isotopes, and which is now isolated from fission products under the name promethium. Hence, *Rydberg* rationalized the phenomenon most incompatible with the "short period" version of the Periodic Table, *viz.* the existence of fifteen consecutive elements having almost the same chemical properties and, surprisingly, exhibiting a far more pronounced similarity than in the triads such as iron, cobalt, and nickel.

The quantum numbers introduced in *Bohr*'s model of the hydrogen atom in 1913 and elaborated by *Sommerfeld* were only intended for atoms containing one electron. However, the regularities found by *Rydberg* in the line spectra of atoms of the alkali metals and of unipositive ions of the alkaline earths strongly suggested that the noble gas atoms form a kind of neutral background (Atomrumpf) to which one external electron (Leuchtelektron) is added. The whole idea of *electron configuration* was not fully clarified by 1923, as can be seen from the commemorative volume of "Naturwissenschaften" published ten years after the Bohr postulates.

We discuss here the quantum numbers n and l introduced according to the quantum mechanics theory of *Schrödinger* and *Heisenberg*[3]; still, it is instructive to make comparisons with the experimental evidence obtained from atomic spectra[4]. According to the "Aufbau principle" the electron configuration consists of the filling of the lowest shells $n\,l$ each capable of containing at most $(4l+2)$ electrons. The trivial symbols s, p, d, f, g, h, ... for $l=0, 1, 2, 3, 4, 5, \ldots$ derive from the former designations of the so-called sharp, principal, diffuse, and fundamental series in the alkali metal line spectra. The main argument for the existence of inner shells stems from X-ray (Röntgen) spectra and, more recently, from photoelectron spectra[5, 6]. Frequently, the positive l-values correspond to two rather different ionization energies, one each for electrons having the quantum numbers $j=(l+1/2)$ and $j=(l-1/2)$. The corresponding relativistic effect ("spin-orbit coupling") is rather weak for external electrons.

The consecutive filling of shells with $(4l+2)$ electrons is in perfect agreement with the observations of *Rydberg*, but, in detail, several irregularities appear. In chemical textbooks, the ground state of the neutral atom is perhaps overemphasized. Firstly, an electron configuration with 2 to $4l$ electrons in a partly filled shell provides several energy levels, which are characterized by different quantum numbers, particularly the total spin S. The main origin of energy differences between such levels is slightly different interelectronic repulsion[3] and it can be shown[7, 8] that a general expression exists for the *spin-pairing energy*,

$$D[\langle S(S+1)\rangle - S(S+1)] \qquad (1)$$

where $\langle S(S+1)\rangle$ is the average value for the partly filled shell l^q. This illustrates one of Hund's rules[4], according to which if more than one value of S is possible ($2 \leqslant q \leqslant 2l$) the highest S corresponds to the lowest energy. Hence, the average energy of an electron configuration (*i.e.* its *bari-*

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center) with partly filled shells is higher than the ground state. Thus, the ground state of the gaseous nickel atom derives from the configuration $[Ar]3d^84s^2$, but the baricenter of this configuration is higher than the baricenter of $[Ar]3d^94s^1$. Secondly, many transition group atoms have energy levels belonging to different configurations, but all lie within 10 percent of their first ionization energy[9]; such energy differences are trivial, when compared with those in the chemical effects to be discussed below.

To a first approximation, the neutral atoms fill their shells in the following order,

$$1s \ll 2s < 2p \ll 3s < 3p \ll 4s < 3d < 4p \ll 5s < 4d < 5p \ll 6s < 4f < 5d < 6p \ll 7s < 5f \ldots \quad (2)$$

where the double inequality signs indicate the noble gas configurations containing 2, 10, 18, 36, 54, 86, ... electrons. Many of the exceptions to (2) are connected with the spin-pairing energy (cf. (1))—*e.g.* when the ground state of the neutral chromium atom belongs to $[Ar]3d^54s^1$ and not to $[Ar]3d^44s^2$. If baricenters are considered, the latter configuration is slightly lower. However, a much more important question is whether 3d or 4s electrons are more stable in the iron group. It might be argued that the presence of two 4s electrons in most of the neutral atoms would indicate that 3d electrons are not preferred, any more than they are in the calcium atom. On the other hand, the 4s electrons are the first to be removed by ionization, and, as a matter of fact[9], all the gaseous ions M^{2+}, M^{3+}, and M^{4+} fill their shells in the order,

$$1s \ll 2s < 2p \ll 3s < 3p \ll 3d < 4s < 4p \ll 4d < 5s < 5p \ll 4f < 5d < 6s < 6p \ll 5f < 6d < 7s \ldots. \quad (3)$$

there being only four exceptions, namely La^{2+}, Gd^{2+}, Ac^{2+}, and Th^{2+}. This apparent discrepancy can be explained by other interelectronic repulsion effects. As example we may consider vanadium, which is the first typical transition element having several oxidation states of comparable stability. Using the energy of the argon core V^{5+} as zero-point of reference, the energies in kK (1 kilokayser $=1000\ cm^{-1}=0.124$ eV $=2.85$ kcal/mole) of the less ionized states are:

		ground state	baricenter
V^0	$[Ar]3d^34s^2$	−1312	−1306
	$[Ar]3d^44s^1$	−1310	−1292
	$[Ar]3d^5$	−1292	−1265
V^{1+}	$[Ar]3d^4$	−1258	−1241
	$[Ar]3d^34s^1$	−1255	−1247
V^{2+}	$[Ar]3d^3$	−1140	−1126
	$[Ar]3d^24s^1$	−1096	−1087
V^{3+}	$[Ar]3d^2$	− 903	− 895
	$[Ar]3d^14s^1$	− 807	− 797
V^{4+}	$[Ar]3d^1$	− 526	− 526
	$[Ar]4s^1$	− 378	− 378

(4)

It should be noted that the calculated values reported in the literature for the consecutive ionization energies have changed considerably with time[9] and, in particular, that the ionization energy of V^{3+} is now known[10] to be 377 kK.

It is possible to construct a model for the tabulated data (4) using a phenomenological baricenter polynomial[11] and to write the average energy of the configuration $(nl)^a(n'l')^b$ containing (a + b) external electrons relative to the closed-shell system:

$$-aI_\varepsilon(nl)-bI_\varepsilon(n'l')+\frac{a(a-1)}{2}A(nl,nl)+abA(nl,n'l')+\frac{b(b-1)}{2}A(n'l',n'l') \quad (5)$$

where $I_\varepsilon(nl)$ is the ionization energy observed for a system containing only one electron in the *nl*-shell outside the closed shells, and where the various *A*-parameters relate to interelectronic repulsion. Assuming $A(3d,3d)=140$ kK, $A(3d,4s)=90$ kK and $A(4s,4s)=70$ kK, and using the observed values $I_\varepsilon(3d)=526$ kK and $I_\varepsilon(4s)=378$ kK, (5) gives the following calculated values (in kK):

V^0	$[Ar]3d^5$	−2630+1400	= −1230
	$[Ar]3d^44s^1$	−2482+1200	= −1282
	$[Ar]3d^34s^2$	−2334+1030	= −1304
V^{1+}	$[Ar]3d^4$	−2104+ 840	= −1264
	$[Ar]3d^34s^1$	−1956+ 690	= −1266
	$[Ar]3d^24s^2$	−1808+ 570	= −1238
V^{2+}	$[Ar]3d^3$	−1578+ 420	= −1158
	$[Ar]3d^24s^1$	−1430+ 320	= −1110
	$[Ar]3d4s^2$	−1282+ 250	= −1032
V^{3+}	$[Ar]3d^2$	−1052+ 140	= − 912
	$[Ar]3d^14s^1$	− 904+ 90	= − 814
	$[Ar]4s^2$	− 756+ 70	= − 686

(6)

This model does not take into account the variation of the radial functions of 3d and 4s on going from V^0 to V^{4+}. Parameters of interelectronic repulsion such as *D* of eq. (1) and *A* of eq. (5) are expected to be proportional to the reciprocal average radius $\langle r^{-1}\rangle$ of the partly filled shell and hence to decrease when the electronic density expands. However, at the same time, I_ε decreases and there seems to be a compensation in neutral l^q systems: $(q-1)A$ and I_ε remain comparable, and the electron affinity of the neutral atom is almost zero. The value calculated for V^{1-} $[Ar]3d^6$ according to eq. (6) is −1056 kK, which suggests spontaneous removal of an electron; this would even be true for $[Ar]3d^44s^2$, with a calculated value of −1230 kK. The values in eq. (6) illustrate the important fact[11] that one-electron energies are not additive in the configuration baricenters. This lack of additivity does not need to be explained by correlation effects, though we must remember that our description of interelectronic repulsion involves phenomenological parameters[8, 12] which are decreased by a kind of inner dielectric effect by a factor of about $(z+2)/(z+3)$ relative to the Hartree-Fock values calculated for a monatomic ion with charge *z*.

Chemistry is very different from atomic spectroscopy in that high oxidation numbers (the highest known being ruthenium(VIII), osmium(VIII), and xenon(VIII)) are frequently stable, whereas the q'th ionization energy of $M^{(q-1)+}$ to M^{q+} tends to be approximately proportional to q (and is $I_\varepsilon-(k-q)A$ when the core is M^{k+}), as long as the same *nl*-shell loses the electrons. The choice of ligands[13] has a great influence on the preferred oxidation state. Thus, vanadium forms the two aqua ions $[V(H_2O)_6]^{3+}$ and $[V(H_2O)_6]^{2+}$ (though the latter is thermodynamically unstable toward hydrogen evolution in aqueous solution) whereas oxo ligands are well-known from the vanadate(V) ion VO_4^{3-} and the vanadyl ion $[VO(H_2O)_4]^{2+}$ (with V^{IV}); finally, carbon monoxide stabilizes the $3d^5$ system vanadium(0) in $V(CO)_6$ and the $3d^6$ system vanadium (−I) in $[V(CO)_6]^-$. There is no apparent connection between these facts and the relationship (4). It is clear that one reason why fluorides and oxides of high oxidation states are known

is that elemental F_2 and O_2 are difficult to form; *Kruck*[14], on the other hand, has shown that phosphorus trifluoride is an excellent ligand for formation of low oxidation states such as $[Ru(PF_3)_4]^{2-}$ and $[Ir(PF_3)_4]^-$ analogous to those in $[Cr(CO)_5]^{2-}$ and $[Fe(CO)_4]^{2-}$

When calculations of the Madelung electrostatic energy of crystals became feasible[15] it was clear that the very high ionization energies of atomic spectroscopy are to a large extent compensated by the electrostatic attraction of the surrounding anions. Actually, the atomic ionization energies even seem to be overcompensated in the sense that many closed-shell cations such as alkali metals M^I, alkaline-earth metals M^{II}, Al^{III}, Sc^{III}, Zn^{II}, Y^{III}, Zr^{IV}, and Th^{IV} represent the only oxidation states of the element considered in non-metallic compounds. It is possible to introduce the concept of *differential ionization energy*[11,16] and to calculate the most stable fractional atomic charges by minimizing the sum of the total interatomic Coulomb (Madelung) energy and a quantity (for each atom) of which the differential quotient is I(z). The function I(z) adapted to eq. (4) for vanadium with the charge z (that is $(5-z)$ electrons in the 3d shell) is (in kK) $-18+75\,z+10\,z^2$.

For many compounds, the minimal energy is obtained for full ionicity with z equal to the oxidation number, whereas in other circumstances, fractional charges between 1 and 2 are predicted for the metallic element. Thus, the central atom in the tetrahedral molecule vanadium(IV) chloride has a fractional charge close to 2. This treatment can be refined by taking into account effects of covalent bonding[11,16] and what is essentially the repulsion between closed-shell cores of adjacent atoms first introduced in the Madelung description by *Born* and *Haber*.

Fajans was the first to emphasize that alkali metal halides (with the exception of lithium salts) dissolve in water with only weak endothermic or exothermic effects. This allows the important conclusion that the sum of the hydration energy of the cation and the anion is almost equal to the Madelung energy of the crystal. The entropy contributions making the difference between enthalpy and free energy are negligible in this connection, and it is possible, for the species which loses one electron, to define the *chemical ionization energy* I_{chem} as the sum of 36 kK (or 4.5 eV) and the product of 8.07 kK and the *standard oxidation potential* U_0. Thus, I_{chem} for $[V(H_2O)_6]^{2+}$ with $U_0=-0.25$ V equals 34 kK. It is possible to discuss the *hydration energy difference*[17] as the difference between the ionization of gaseous $M^{(z-1)+}$ and I_{chem} of the aqua ion, whose oxidation number changes from $(z-1)$ to z. This *hydration energy difference* can be written to a good approximation as:

$$I_z - I_{chem} = \kappa(2z-1) \qquad (7)$$

where the parameter κ is close to 45 kK for beryllium(II) and aluminum(III), 43 kK in the 3d series, 35 kK in the 4f series, and about 31 kK in the 5f series. Expressions of type (7) would also be obtained for the hydration, if it could be represented as the introduction of an ion with radius r_{ion} into a perfect dielectric medium. In this case $\kappa = 57$ kK/r_{ion} if r_{ion} is measured in Å and differential effects of changing ionic radius during the ionization are neglected. *Latimer*[18] pointed out that such an interpretation works well for anions, but that cations seem to have r_{ion} values some 0.8 Å larger than the conventional ionic radii. In any case, κ decreases with increasing radii in the case of the heavier elements. Hence, I_{chem} for $[Ti(H_2O)_6]^{3+}$ (36 kK) is smaller than for cerium(III) aqua ions (51 kK), though I_4 for Ti^{3+} is 349 kK and for Ce^{3+} only 296 kK. The sub-shell energy difference in octahedral complexes of 3d elements is sufficiently large (8 to 20 kK) for "ligand field stabilization" effects to be detected in the apparent irregular variation of the U_0 values for hexaaqua ions[19,20].

It might be argued that hydroxo and oxo complexes are formed by deprotonation of known or hypothetical aqua ions, and that the theory of hydration energy difference can readily be extended to such systems. However, in view of the known I_{chem} values of 41 kK for RuO_4^{2-} and 44 kK for RuO_4^- in aqueous solution, it is not easy to obtain a reliable connection with the very large I_7 and I_8 for gaseous ruthenium ions, and it is doubtful whether it could have been possible to predict the existence of the perxenate anion XeO_6^{4-} in this way.

There is not the slightest doubt, however, that no simple relation exists between the electron configuration of the ground state of the neutral atom and the chemistry of the element under consideration. Thus, iron and ruthenium differ much more from each other chemically than do nickel, palladium, and platinum, though the configurations are analogous ($[Ar]3d^64s^2$ and $[Kr]4d^65s^2$) in the former case but differ ($[Ar]3d^84s^2$, $[Kr]4d^{10}$, and $[Xe]4f^{14}5d^96s^1$) in the latter. The most spectacular discrepancy between the spectroscopic and chemical versions of the Periodic Table is that helium is an alkaline earth element from the point of view of atomic spectroscopy, since its ground configuration does not terminate with np^6 like the other noble gases. Hence, it is not too surprising that the almost invariant trivalency of the lanthanum series has little to do with the ground states of the neutral atoms.

Hund[4] believed that these atoms have three valence electrons $[Xe]4f^q5d^16s^2$. However, this is only true[21] for lanthanum, cerium, gadolinium, and lutetium (which can most conveniently be considered as the first member of the 5d series), whereas the atoms of the remaining eleven lanthanoids have ground states belonging to $[Xe]4f^{q+1}6s^2$ and are really barides (baroids) from this point of view. The reason for the almost constant trivalency in the 4f series differs from that for the trivalency of aluminum, where the Madelung potential[15] or other chemical stabilizations cannot compensate the very large I_4 of 968 kK necessary for removing a 2p electron from the neon core, whereas an added electron would enter the loosely bound 3s orbital. It was first pointed out by *Connick*[22] in a comparative study of standard oxidation potentials that the *electron affinity* of a partly filled 4f shell is much smaller than the ionization energy because of interelectronic repulsion effects such as $A(4f,4f)$ in eq. (5). This explains why a definite number of 4f electrons may be much more stable, in analogy to eq. (6), and why for sufficiently low ionic charges, it is necessary to have one or two 5d and 6s electrons present. Thus, the cerium atom ground state $[Xe]4f^15d^16s^2$ ionizes to gaseous $Ce^{2+}[Xe]4f^2$, though a low concentration of Ce^{II} in CaF_2 has the ground configura-

tion[23] $[Xe]4f^15d^1$ and excited levels of configuration $[Xe]4f^2$. Incidentally, these solid solutions containing Ce^{II} or Gd^{II} are among the rare case of *two* partly filled shells in chemistry, other examples being gaseous molecules such as TiO, whose ground state[24] is closely related to the configuration $[Ar]3d^14s^1$. At the other end of the 4f series, the closed systems $[Xe]4f^{14}$ form the ground state (well below the first excited level) of gaseous Yb^{2+}, Lu^{3+}, Hf^{4+},

and the corresponding ytterbium(II), lutetium(III), hafnium(IV), tantalum(V), ... compounds. Other $[Xe]4f^{14}$ systems are unstable, but in analogy to (6), because of a high $A(4f,4f)$, the neutral erbium atom has the configuration $[Xe]4f^{12}6s^2$, that of free Er^{2+}, like Er^{II} in the fluorite lattice have the configuration $[Xe]4f^{12}$, and free Tm^+ has the configuration $[Xe]4f^{13}6s$.

Addition of a 4f electron to M^{III} to give M^{II}, or removal of a 4f electron to give M^{IV} requires an energy which varies in a characteristic way with the number of 4f electrons. This variation can be obtained by an extension of eq. (1) to include further, smaller effects of interelectronic repulsion and first-order relativistic effects. It was first used[25] to explain the variation of the electron transfer spectra[26] of bromides in nearly anhydrous ethanol and of dialkyldithiocarbamate complexes. Later studies included the variation of $4f^q \rightarrow 4f^{q-1}5d^1$ transitions in M^{II}[27] and M^{III} systems[28] in fluorite lattices, the variation of standard oxidation potentials[29], and electron transfer spectra of hexachloro, hexabromo[30], and hexa-iodo complexes[31] of trivalent lanthanoids. All of these applications refer to the change of one 4f electron, but direct evidence for a slight chemical variation of the considerable amount of spin-pairing energy (1) having a minimum for $q=7$ and $S=7/2$ (with $D=6.5$ kK) was obtained[32, 33] from the "tetrad effect" which was first discovered by *Fidelis* and *Siekierski* by careful studies of equilibrium constants. Only recently has it been possible to determine the ionization energies of 4f electrons in compounds of rare-earth metals[34, 35] and in the subsequent compounds[36] of Hf, Ta, W, Re, ... by photoelectron spectrometry, whereby solid samples were bombarded with 1486.6 eV photons from an aluminum anticathode. Though it is well established from the *nephelauxetic effect*[11, 37] (the interelectronic repulsion changes only 5 percent in the transition from free Pr^{3+} to praseodymium(III) compounds and, in generally, only 1 to 2 percent between different compounds of the same M^{III} systems having from two to twelve 4f electrons) that the covalent bonding of the 4f shell produces only a very weak (radial) expansion and delocalization (which can be treated by the *angular overlap model*[38, 39]), it is remarkable that the ionization energy of the 4f shell is comparable or slightly larger (between 11 and 18 eV) than that of the ligand orbitals. This finding is not surprising when it is remembered that the electron affinity of the 4f shells is far smaller because of interelectronic repulsion; nevertheless, it casts some doubts whether the diagonal elements in a Hückel-Wolfsberg-Helmholz type model can be identified with orbital ionization energies[8].

Now that the internal mechanism of the lanthanoids is better understood it is recognized that the trivalency is to some extent an accidental result of the numerical parameters of hydration energy (7), whereas an almost invariant oxidation number is a more general consequence of a large difference between the electron affinity and ionization energy (such as is true also for beryllium or aluminum).

In the specific case of a partly filled shell the magnitude of A in eq. (5) is considerably greater than that of 2κ in eq. (7).

The chemistry of protactinium and of uranium is, in certain respects, different from that of tantalum and tungsten, but at least these elements most frequently have the oxidation states Pa^V and U^{VI} corresponding to the closed-shell configuration of 86 electrons in radium(II) and actinium(III). Around 1925, very little doubt was expressed about the 5f group beginning somewhere among the unknown elements following uranium. Exactly as for the three valence electrons of lanthanoid atoms, it was felt (without direct spectroscopic evidence) that the very line-rich arc spectrum of uranium belonged to an atom with the ground configuration $[Em]6d^47s^2$ (symbolized Em, "emanation"; radon is, for the writer, merely the name of an isotope like deuterium). However, the geochemist *Goldschmidt* suggested that thorium starts a new series of mainly quadrivalent rare earth elements. This proposal was mainly based on the existence of the oxides MO_2 (now known for M = Th, Pa, U, Np, Pu, Am, Cm, Bk, and Cf), which crystallize in the particularly stable fluorite lattice with a high Madelung energy. Much more interesting for us is the fact that *Ephraïm*[40] found the narrow absorption bands of several uranium(IV) compounds which are, in close analogy to praseodymium(III) compounds[11], indicative of the configuration $[Em]5f^2$. Unfortunately at that time, it could not be argued convincingly that only partly filled f shells produce narrow absorption bands in samples in the condensed state (crystalline, vitreous, or liquid). Certain 3d group central atoms, such as the chromophore $Cr^{III}O_6$ of ruby or the isoelectronic MnF_6^{2-} ion, have excited levels producing narrow absorption (and frequently line luminescence) bands belonging to the same sub-shell as the ground state. Hence, the excitation energy is mainly due to interelectronic repulsion being more pronounced in the excited state (as in the f groups), while the electronic density remains practically unchanged in three-dimensional space. It is interesting to note that the first application of *Bethe*'s electrostatic ligand field approach (nonspherical part of the Madelung potential) to visible spectra was carried out by *Finkelstein* and *Van Vleck*[41], who found the narrow, spin-forbidden ($S=3/2 \rightarrow S=1/2$) intra-sub-shell transitions in ruby and complained that the spin-allowed transitions between the lower and the upper sub-shell were hidden by broad coincident absorption bands. *Tanabe* and *Sugano*[42] later pointed out that it is simply these transitions that produce the broad bands, since the equilibrium internuclear distances are larger in the excited states containing an anti-bonding 3d electron. Hence, in this case, the Franck-Condon principle, which describes the superposition of vibrational coexcitation on the electronic transition, comes into operation[8].

As described in the Gmelin volume, "Uranium", it was originally thought that the fission products obtained by neutron bombardment were transuranium elements. However, when neptunium was identified by *McMillan* and *Abelson* in 1940, its chemical properties appeared so similar

to those of uranium that it was felt that the beginning of a 5f series, designated *uranides* had been discovered. *Seaborg* collaborated in the discovery of the subsequent eight elements and became more and more convinced that the transuranium elements, like the rare earths, tend toward trivalency; he therefore suggested the designation "*actinides*" (now called actinoids according to IUPAC rules) for the 5f elements. During the second world war, *Spedding* developed the technique of ion-exchange for the separation of elements of the lanthanum series. This technique proved to be a much more convenient and rapid method of separation than fractional recrystallization for the separation of such elements. Assuming that the new elements Am, Cm, Bk, Cf, Es, and Fm also exist in solution as M^{III} aqua ions, the same method of separation was resorted to and it became possible to separate and identify them. It must be remembered that at the time of their discovery, such elements were available in quantities ranging from only 10^{16} atoms (a few micrograms) down to 10^6 atoms.

As the chemistry of the transuranium elements was further developed[43,44] it was soon realized that the true situation was not quite so simple. Uranium, neptunium, and plutonium all assume the oxidation states M^{III}, M^{IV}, M^{V}, and M^{VI}. This turned out to be true also for americium, although in this case no hexafluoride could be prepared, but only the americyl ion AmO_2^{2+}. These linear dioxo complexes must be particularly stable; the electron transfer band does not occur at very low wave numbers (not much below that in the blue region of UO_2^{2+} which usually is luminescent and had contributed to the somewhat accidental discovery of radioactivity in 1896). Curium, berkelium, and californium are most stable as M^{III}, but can also occur as M^{IV} in the form of oxides and fluorides. The position of the electron transfer band of orange $BkCl_6^{2-}$ has been determined[29]. Only the M^{III} state is definitely known in the case of einsteinium and fermium; however, it cannot be argued any longer that only positive deviations from M^{III} occur at the beginning of the 5f series. It was shown by tracer experiments[45] that mendelevium(III) can be reduced to a species similar to europium(II)[*]; the standard oxidation potential, however, is $U_0 = -0.1$ V. This is a most striking difference from the Am^{II} system, which must be far more strongly reducing. This trend at the end of the 5f series could be predicted immediately the electron transfer bands of californium(III) and einsteinium(III) bromo complexes in ethanol had been detected[46]. Nobelium(II) aqua ions ($Z = 102$) are exceedingly difficult to oxidize in aqueous solution. On the other hand, dark green neptunium(VII) and dark blue plutonium(VII) oxo complexes (of type MO_5^{3-} or perhaps in the form of mixed hydroxo-oxo complexes with additional water of constitution) represent species with unexpectedly high oxidation states[47] in the beginning of the 5f series; in the meantime the crystal structures of systems containing such anions[48] and of Li_5MO_6, which is isotypic[49] with the previously known orthoperrhenate(VII) Li_5ReO_6, have been determined.

Recent progress in the chemistry of the transuranium elements clearly shows that the 5f series has the same relation to the 4f series as has the 4d (palladium) group to the 3d (iron) group[17]. At the beginning of the series one finds species such as MoO_4^{2-} and TcO_4^-, which are far less oxidizing than CrO_4^{2-} and MnO_4^-, and the volatile compounds RuF_6, RuO_4, and RhF_6, for which there are no analogies in iron and cobalt chemistry. On the other hand, at the end of the group, we have silver(I), which is much more difficult to oxidize than copper(I). Such a difference between a group with rather low and constant oxidation number (as in the 3d and 4f group, where $n = l+1$, and the radial function has no nodes) and a group in which the oxidation number varies from high at the beginning to low at the end (as in the 4d, 5d, and 5f groups, where n is larger than $(l+1)$) can be described[50] by the parameter $(E-A)$. This parameter was first introduced[25,26] to indicate the more or less steeply increasing oxidizing character of the central atom in a given transition series, when the oxidation state is kept constant. It is the difference between the more negative one-electron energy E, when the central field is changed by increasing the atomic number Z by one unit, and the increased interelectronic repulsion A due to the presence of an additional electron in the partly filled shell. In other words: in strongly screened systems, $(E-A)$ is small and has a value close to 2.9 kK for trivalent lanthanoid complexes having various ligands; a value of 8 kK is obtained when derived[19] from the standard oxidation potential of M^{II} hexaaqua ions of the 3d elements and 8.5 kK when derived from M^{III} aqua ions of the 5f elements[29]. When $(E-A)$ is small, as in the 3d and 4f groups, the tendency toward invariant oxidation number is pronounced, whereas a large value of $(E-A)$ produces high oxidation numbers at the beginning and low oxidation numbers at the end of a given transition series. This is the reason why the writer does not recommend the word "actinide" and would rather speak of a 5f group or a group of transthorium elements.

There is no intrinsic contradiction[51,52] between the presence of 5f electrons and the high and varying oxidation states for Z between 91 and 98. The spectroscopic properties of M^{III} systems and higher oxidation states in compounds are unconditionally in favor of the presence of 5f electrons besides the closed-shell emanation core. The manifest chemical differences between the chemistry of protactinium and praseodymium, and between uranium and neodymium, are of the same kind as the "chemical" difference between beryllium and helium seen from the point of view of a spectroscopist. There is a difference between the neutral thorium atom and the cerium atom, insofar as the ground state of the former atom[53] corresponds to the configuration $[Em]6d^27s^2$, whereby the element constitutes a higher homolog of zirconium. Th^{2+} is a particularly interesting system[54,55] in that the ground state corresponding to $[Em]6d^2$ is followed within 0.81 kK by the first level of the $[Em]5f^16d^1$ configuration. Actually, the baricenters (in kK relative to the ground state) are:

$[Em]6d^2$	6.6	$[Em]6d^17s^1$	7.2
$[Em]5f^16d^1$	9.5	$[Em]5f^17s^1$	5.4
$[Em]5f^2$	24.4	$[Em]7s^2$	11.9

(8)

There are reasons[56] for assuming the ionization energy of Th^{2+} to be 150 kK. When this estimated value is combined

[*] *Note added in proof:* Meanwhile mendelevium(I) has also been detected [73].

with the known I_s values of 228 kK for 5f, 219 kK for 6d, and 208 kK for 7s in Th^{3+}, the parameters of interelectronic repulsion of eq. (5) are as follows:

$$\begin{array}{ll} A(5f, 5f) = 102 & A(5f, 7s) = 63 \\ A(5f, 6d) = 78 & A(6d, 7s) = 56 \\ A(6d,6d) = 67 & A(7s, 7s) = 50 \end{array} \quad (9)$$

The increase in average radius in the series $5f < 6d < 7s$ is seen to have the same effect in the tabulated list (9) as the series $3d < 4s$ in eq. (6). It can now be understood why 5f electrons in the case of thorium are stabilized only at high ionic charges. The situation is more clear-cut in the case of uranium, where the ground state of the neutral atom derives from $[Em]5f^36d^17s^2$, and where the three 5f electrons remain in uranium(III) compounds. The general opinion today is that the ground state of neutral Pa, U, Np, and Cm belong to $[Em]5f^q6d^17s^2$ and of Pu, Am, Bk, and subsequent elements to $[Em]5f^{q+1}7s^2$. However, as we have seen, this has little bearing on chemical behavior, and there is no doubt that the narrow absorption bands of M^{III} compounds are due to transitions within the configuration $[Em]5f^q$, whereas broad, intense bands due to $5f \rightarrow 6d$ transitions are known to occur in many compounds of Pa^{IV}, U^{III}, U^{IV}, Np^{III}, Np^{IV}, Pu^{III}, Pu^{IV}, Am^{III}, Bk^{III}, *etc.*[11, 29, 46, 51, 57].

Herrmann and *Seyb*[58] and *Keller*[44] discuss the possibilities of preparing heavier elements. In practice, this has until recently been carried out by bombarding gram quantities of plutonium or curium with oxygen or neon ions in electrostatic accelerators. The leading research groups in Berkeley (California) and Dubna (Russia) have obtained thousands, or only hundreds, of atoms of the elements 103, 104, and 105. The study of these elements necessitates the use of subtle techniques previously unresorted to in chemistry, even on an ultramicro-scale. Despite their short half-life, in some cases only a few seconds, their behavior has been studied by carrying out volatility experiments with anhydrous chlorides of other elements. There is no doubt that 102^{II}, 103^{III}, 104^{IV}, and 105^{V} have the closed-shell configuration $[Em]5f^{14}$ in analogy with $[Xe]4f^{14}$ of hafnium(IV) compounds *etc.* It is highly probable that elements 106, 107, and 108 can also occur in their highest oxidation states VI, VII, and VIII; the higher ionic radius of element 108 would suggest octahedral coordination as being plausible in the MO_6^{4-} system or in mixed hydroxo-oxo complexes—as is already known[13] in the osmate(VI) system $[OsO_2(OH)_4]^{2-}$. It is more difficult to ascertain whether element 109 could achieve the as yet unknown oxidation state IX.

A few years ago, the hope of making trans-105 elements seemed very remote because of the rapidly decreasing yields (extrapolating to less than an atom per experiment) and half-lives. The main difficulty is the pronounced deficit of neutrons obtainable by normal nuclear reactions; even high-flux neutron sources and subterraneous nuclear explosions do not seem to lead to formation of elements beyond fermium. However, it has been known since 1948, when *Maria Goeppert-Mayer* and *Hans Jensen*[59] published their nucleonic shell model, that certain numbers N of neutrons or Z of protons form particularly stable nuclei; well-known examples are oxygen 16, calcium 40, zirconium 90, and lead 208, which have both N and Z belonging to the class of nucleonic, closed shells 8, 20, 40, 50, 82, and 126. All isotopes of the elements immediately following lead, namely Po, At, Em, and Fr, have particularly short half-lives, while several isotopes between Th and Cm have longer half-lives. The next possible closed proton shell would be at $Z = 114$ and theoreticians believe that several isotopes of 112, 133, and 114 may have half-lives (the main decomposition mode being spontaneous fission) around $10^{5\pm4}$ years, the upper limit bringing them into the range of geochemical possibilities.

The tungsten bricks employed to stop the 24 GeV protons generated at CERN (near Geneva) have been recently studied[60] and an added trace of inactive mercury was found to trap a highly unusual isotope which undergoes spontaneous fission and emits high-energy α-particles. Some skepticism was expressed as to whether this isotope really is eka-mercury ($Z = 112$) and it has recently been shown[61] that two-thirds of the activity is due to californium 252. It is not yet known whether this is an unexpected impurity or an ingrowing daughter. Be that as it may, the origin of the remaining activity cannot be explained this way; unusual properties have to be accounted for; the fission does not seem to be binary but may be ternary or of a higher order. One has to be somewhat cautious; several isotopes of elements between thorium and curium have metastable isomers with much larger ellipticity than the ground state and correspondingly shorter half-lives relative to spontaneous fission[62]. Fortunately, the suspected eka-mercury has a half-life of longer than six months, possibly of several centuries. Quite recently, in the laboratory at Orsay (near Paris), thorium has been bombarded with 500 MeV Kr^{24+} ions and unknown α-activities of 13 to 15 MeV have been detected[63].

It is generally agreed[64, 65] that eka-lead ($Z = 114$) is a more volatile metal than lead and that the 114^{II} aqua ion must be stable in aqueous solution, though "soft" sulfur-containing ligands and iodide also ought to be strongly coordinated and could favor the formation of higher oxidation numbers, such as those of the $6d^8$ system 114^{VI}. According to *Rydberg*, element 118 should be a noble gas, but it has already been pointed out by *Grosse*[66] that this element possibly exists as a semimetal, which, like mercury, is converted into a monatomic gas on evaporation. Recent developments in the chemistry of xenon[67, 68] show that there is little doubt that 118^{IV} should be fairly stable. Unfortunately, this element cannot be observed because of its nuclear properties.

In the region of the Periodic Table considered here, the relativistic effect that s orbitals (and with smaller probability $p_{1/2}$ orbitals) have a finite density at the nucleus producing an electrodynamic stabilization becomes chemically important. This effect may already contribute to the well-known preference for the oxidation states Tl^{I}, Pb^{II}, and Bi^{III} and manifests itself most clearly in the spectroscopic finding that the ionization energies of gaseous Ra and Ra^+ are just slightly larger than those of Ba and Ba^+. Correspondingly, the two 8s electrons of the atom

with $Z=120$ are more strongly bound than the outermost s electrons of radium.

Though the number 126 may correspond to a well-established closed shell of neutrons, it is less probable that it is a closed shell of protons. Many Dirac-Fock calculations have been performed on neutral atoms having Z between 121 and 130, and the relative occupation numbers estimated for the 8s, 8p, 7d, 6f, and 5g shells deviate from one another substantially[69]. However, for the chemist, the important point is that the average radius of the 5g shell is very small and the difference between ionization energy and electron affinity correspondingly very large. As we have seen above, this situation favors a fixed oxidation state in compounds of such elements, and it has been suggested[50] that the most likely candidate is 126^{IV} with the electron configuration $[118]5g^4$. This would make its chemistry rather similar to that of thorium(IV), and macroscopic amounts should therefore be strongly colored because of the many low-lying excited levels of the configuration $[118]5g^36f^1$.

If the nucleus was a point, the Dirac treatment for Z above 137, *i.e.* for the reciprocal fine-structure constant, would be divergent. However, when the finite radius and the approximately invariant density of the nucleus are taken into account[70], finite ionization energies somewhat larger than the non-relativistic Hartree-Fock values are found. The next candidate for a closed proton shell would have $Z=164$. Extrapolation of the series (2) would give the ground configuration $[118]5g^{18}6f^{14}7d^{10}8s^28p^2$ for dwi-lead (which is called "zwei-blei" in New Mexico) in agreement with Dirac-Fock calculations[71, 72]. However, a major difference from lead is the relativistic stabilization of the 8s and $8p_{1/2}$ electrons, whose ionization energy ought to exceed that of several other orbitals. It is suggested that the 164^{II} aqua ion contains the partly filled shell $7d^8$ besides the other electrons of the free atom. This would make the chemistry closely analogous to that of palladium(II), the hydration energy differences being determined by the consecutive ionization energies of the 7d shell[72]. The atoms condense to a fairly noble metal, similar to the palladium atoms in the closed-shell configuration $[Kr]4d^{10}$.

An extrapolation according to *Rydberg* suggests the next noble gas as being at $Z=168$. It is definitely known that such a situation does not occur before $Z=172$, since the following orbitals 9s and $9p_{1/2}$ are stabilized for relativistic reasons. A closed proton shell may occur at $Z=184$. This element contains a partly filled 6g shell. If one can extrapolate[8] from the lower transition series with $n=l+2$, one would expect varying oxidation states from 184^{IV} with the configuration $[172]6g^8$ (perhaps stabilized if the relativistic separation between the eight $6g_{7/2}$ and the ten $6g_{9/2}$ electrons is large) to 184^{XII} with the closed-shell [172] configuration, which could perhaps form a volatile hexoxide or fluoro-cations such as $(184)F_8^{4+}$. If this hypothesis were correct, element 184 would be a super-ruthenium with its oxidation state changing by many units like that between Ru^{-II} with $[Kr]4d^{10}$ and Ru^{VIII} with $[Kr]4d^0$ However, *Fricke* and *Waber* have suggested a smaller average radius of the 6g shell favoring a constant oxidation number. This is a question to some extent determined by eq. (7), though strong effects of polarization and Van der Waals attraction (cf. the high sublimation temperature of WCl_6) and high formation constants of complexes with "soft" ligands (according to *Pearson*) could necessitate modification of this simple description.

Fricke, *Greiner*, and *Waber*[71] have questioned whether the Dirac treatment becomes divergent when the one-electron eigenvalues E (which are slightly below mc^2 in light atoms by an amount corresponding to the ionization energy found by X-ray or photoelectron spectra) approach $-mc^2$ for the 1s orbital at $Z\approx174$ and for the $2p_{1/2}$ orbital at $Z\approx190$. The point is that for the "Dirac sea", an overall equally dense continuum of one-electron functions, all E values lie below $-mc^2$. The Dirac interpretation of a positron as a hole in this continuum which is capable of annihilating an electron and forming the conventional vacuum. This question is related to the problem whether in Nature a higher limit exists for electric field strength, a dielectric screening being introduced by the formation of positron-electron pairs. The writer is not an expert regarding this subject but would like to suggest that the risk of divergence would occur only for the much higher Z^* values for which the *total energy* (which, after all, is the quantity minimized in Hartree-type models) approaches $-Z^*mc^2$. For lighter atoms, the total energy including the rest-mass of the electrons is approximately

$$(2\cdot137^2Z - Z^{2.4}) \text{ rydberg units} \qquad (10)$$

But this is a non-relativistic result, valid only for Z below 100. The electron cloud is entirely different from the atomic nucleus, the two 1s electrons contributing a significant amount, almost $-2Z^2$ rydberg units, of the total binding energy.

Some concern has been expressed among nuclear theoreticians as to whether the very heavy nuclei conserve their spherical or moderately ellipsoidal shape[62]. It is conceivable that nuclei may develop cavities and become positively charged bubbles. In such a case, the usual nucleon shell model[59] would no longer be applicable. Nevertheless, it would still be possible that quite definite combinations of Z and N would have particularly long half-lives.

From the practical point of view of how to attempt to make an element with Z above 120, the major problem is the neutron deficit of the starting materials; it is quite possible that the only solution is a supernova explosion or cutting a slice of a neutron star. It is instructive, however, for conventional inorganic chemistry that only a very loose and very sophisticated relation exists between the ground electron configuration and the chemical properties of a given element. If we are ever going to hunt one of the trans-105 atoms, we shall never be in the fortunate situation enjoyed by those who sought promethium, where it was known since the time of *Moseley* that the chemical properties would lie very accurately between those of neodymium and samarium. Actually, the higher ionic charges are, considering eq. (7), of greater interest than are the neutral atoms, and the whole question of selection of oxidation state[11] is far better understood today than it was just a few years ago.

Discussion between physicists, who like beautiful but oversimplified treatments, and chemists, who swim in complexity, is nevertheless occasionally fruitful.

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Semiempirical Use of Chirality Functions[1a, 1b] for the Description of the Optical Activity of Allene Derivatives in the Transparent Region

By Ernst Ruch, Wolfgang Runge, and Günter Kresze[*]

A comparison of calculated and experimental data shows that the optical rotatory power of phenylallenecarboxylic acids is quantitatively described by the polynomial expression developed in (1). The T_d component of this expression, the only relevant one for the case of methane derivatives turns out to be negligibly small in the case of allene derivatives. Therefore, and because allene derivatives belong to category a[16] the sequence of the λ-parameter values of the ligands may be used to determine the configuration and the sign of rotation.

1. Theoretical

The rotation of the polarization plane of polarized light upon passing through a non-racemic mixture of chiral molecules in an achiral solvent is a special example of a chirality observation. Chirality observation as generally defined is the measurement of numerical values of objects (or mixtures thereof) with experimental devices, leading to the value zero if the object is achiral (or the mixture racemic) and to identical numbers with opposite signs if the objects or mixtures are enantiomeric.

Chirality observations provide structural insight, and chirality functions, serving as mathematical expressions, represent this structure in a lucid form if we study the chirality of molecular classes defined as follows. A molecular class contains molecules with a common achiral skeleton and varying achiral ligands at given skeleton sites. We supplement this definition by an additional restricting condition, namely that the manner in which a ligand is attached does not depend upon the nature of the neighboring ligands, and molecules with exclusively identical ligands have the symmetry of the skeleton. This requirement implies a certain selection of permitted ligand types. The ligands must be of such a kind and fixed in such a manner that symmetry operations of the skeleton belonging to the subsymmetry of a fixed site are also symmetry operations of the corresponding ligand. Insofar as deviations from this condition have little influence on the result of the measurement, they may be treated as a perturbation. An essentially algebraic theory applicable to any type of chirality observation and any class of molecules of the type mentioned was presented in ref.[1a] and has been outlined recently without mathematical details in a review[1b]. The results present three different aspects for the chemist:

1. For the forementioned classes of molecules, the theory yields a structural concept for the chirality phenomenon corresponding in nature and significance to the concept of symmetry in spectroscopy.

2. Thus it also provides structural clues for a quantum-mechanical or classical treatment of particular chirality observations of such molecules.

3. In the form of special expressions[1,2] characterized by mathematical simplicity, semiempirical methods for the calculation of chirality observations can be proposed. Only formally defined elements of the expression, such as ligand-specific parameters *etc.*, are determined experimentally and may be interpreted physically *a posteriori* if desired. The quantitative description of a chirality observation by a chirality function naturally guarantees the theoretical determination of the configuration of a molecule.

It is the last-mentioned aspect 3, in particular, which we treat here by testing the quantitative description of the optical rotation of allene derivatives. However, statements of the general theory concerning our particular problem will be sketched first so that the reader may obtain a better understanding of the relationship between our experimental arrangements and the theoretical questions.

The algebraic analysis allows us to establish exactly which additional properties a chirality function must also have in order to be different from zero, in principle, when applied to any possible non-racemic mixture of isomers. A chirality function of this type has been called "qualitatively complete". This requirement arises from reservations concerning the quality of specific expressions for chirality functions. This problem may differ from one molecular class to another, but disappears in any case if the expression has the property mentioned above[1a]. It should be pointed out that nearly all the existing theories of optical activity fail to satisfy this requirement. It is found that the "qualitatively complete chirality function" for a class is made up additively of components with different structures. In the case of a molecular class with ligand sites at

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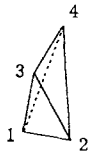
the corners of a tetrahedron of symmetry D_{2d}, corresponding to allene derivatives, there are two such components.



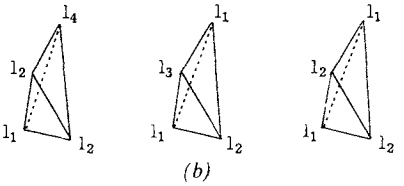
(a)

We write the qualitatively complete chirality function $\varphi(l_1, l_2, l_3, l_4)$ depending on some parameters for each ligand on skeleton sites 1, 2, 3, and 4 (compare *(a)*) in the form:

$$\varphi(l_1, l_2, l_3, l_4) = \varphi_1(l_1, l_2, l_3, l_4) + \varphi_2(l_1, l_2, l_3, l_4) \quad (1)$$

The structures of the two components φ_1 and φ_2 can be found from the general theory[1a]. We confine ourselves to stating here the consequences which can be verified on the particular qualitatively complete chirality function (3).

The function $\varphi_2(l_1, l_2, l_3, l_4)$ vanishes if two of the ligands are identical, a fact which seems surprising in the case of chiral molecules of type *(b)*.



(b)

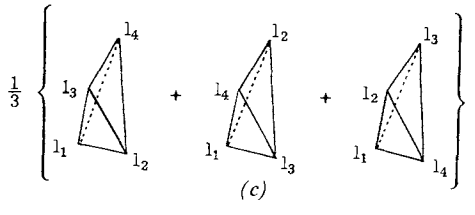
The function $\varphi_1(l_1, l_2, l_3, l_4)$ satisfies the zero identity:

$$\varphi_1(l_1, l_2, l_3, l_4) + \varphi_1(l_1, l_3, l_4, l_2) + \varphi_1(l_1, l_4, l_2, l_3) \equiv 0 \quad (2)$$

Therefore it does not contribute to the expression

$$\tfrac{1}{3}\{\varphi(l_1, l_2, l_3, l_4) + \varphi(l_1, l_3, l_4, l_2) + \varphi(l_1, l_4, l_2, l_3)\}$$

which describes the chirality observation of a non-racemic isomer mixture of the type shown in *(c)*, if we assume linear superposition of contributions from the single compounds in this mixture.



(c)

Two special types of chirality functions have been developed[1,2] which can be used for semiempirical purposes. One type of function consists of polynomials of lowest degree in ligand-specific parameters for each component. The expression needed here is a sum of polynomials denoted by $\chi(l_1, l_2, l_3, l_4)$ and it has the form:

$$\begin{aligned}\chi(l_1, l_2, l_3, l_4) = {} & \varepsilon_1[\lambda(l_1) - \lambda(l_2)][\lambda(l_3) - \lambda(l_4)] \\ & + \varepsilon_2[\mu(l_1) - \mu(l_2)][\mu(l_2) - \mu(l_3)][\mu(l_3) - \mu(l_1)] \\ & \times [\mu(l_1) - \mu(l_4)][\mu(l_2) - \mu(l_4)][\mu(l_3) - \mu(l_4)]\end{aligned} \quad (3)$$

The λ- and the μ-polynomial evidently have the above-mentioned properties of φ_1 and φ_2. The parameters λ and μ can be determined either on the basis of a quantum-mechanical treatment from which they also receive their physical interpretation, or from optical activity measurements. The coefficients ε_1 and ε_2 are sign factors $+1$ or -1, which are the same for all molecules of the class, and can also be found quantum-mechanically or experimentally. Molecules of type *(b)* or isomer mixtures of type *(c)* represent experimental arrangements where an optical activity measurement depends only upon one kind of parameter in our expression (3). This can be seen from equations (4) and (5):

$$\chi(l_1, l_2, l_2, l_4) = \varepsilon_1[\lambda(l_1) - \lambda(l_2)][\lambda(l_2) - \lambda(l_4)] \quad (4)$$

$$\begin{aligned}\tfrac{1}{3}\{\chi(l_1, l_2, l_3, l_4) + \chi(l_1, l_3, l_4, l_2) + \chi(l_1, l_4, l_2, l_3)\} \\ = \varepsilon_2[\mu(l_1) - \mu(l_2)][\mu(l_2) - \mu(l_3)][\mu(l_3) - \mu(l_1)] \\ \times [\mu(l_1) - \mu(l_4)][\mu(l_2) - \mu(l_4)][\mu(l_3) - \mu(l_4)]\end{aligned} \quad (5)$$

The transformation properties of the two component functions allow a further physical interpretation.

In the case of a skeleton having regular tetrahedral symmetry, the mixture of type *(c)* represents a chiral molecule in three different positions. Therefore the chirality function for derivatives having a skeleton of symmetry T_d must remain unchanged if applied to the mixture of type *(c)*. Thus it follows from (5) that the λ-polynomial vanishes in this case and the μ-polynomial then represents the qualitatively complete chirality function for this class. On the other hand, with increasing deviation from T_d-symmetry, the λ-component becomes increasingly more important. It describes ultimately the relevant part of the phenomenon.

In the case of methane derivatives we certainly have one limiting case of a skeleton with the symmetry of a regular tetrahedron. Allene derivatives on the other hand may possibly represent the opposite situation, because the allenic double bonds form the chromophore skeleton undergoing strong interactions with light and these very definitely differ from the T_d-symmetry. The conjecture that the μ-polynomial may be very small, negligible perhaps relative to the λ-component, follows also from the quantum-mechanical theory[3].

This conjecture can be checked experimentally.

First, the optical rotation of an isomer mixture of type *(c)*, *i.e.* the arithmetic mean of the rotations of the individual components of the mixture, should be zero or at least small in relation to the rotations of the individual compounds if our assumption is correct.

Secondly, chiral allene derivatives having one or two pairs of like ligands exhibit pronounced optical activity. This means that the λ-component makes substantial contributions. Therefore we calculate the λ-parameters of ligands from the optical data of corresponding compounds. The question whether the μ-component may be neglected,

i.e. whether the "shortened approximation" yields quantitatively adequate information, can be answered if the optical rotation of allene derivatives having four different ligands can be calculated with sufficient accuracy from the derived λ-parameters alone.

Our λ-polynomial is formally identical with a formula given by *Brewster*[4] which is derived from an analogy with the interaction of spirals with plane-polarized light. The Brewster formula, however, contains physically prejudiced parameters. Its use necessitates that the polarizabilities of the ligands be known. Its scope is limited by the greatly simplified model.

If our formula in the qualitatively complete equation (3) or in the shortened form (4), *i.e.* neglecting the μ-polynomial, is quantitatively confirmed for a number of allene derivatives appreciably greater than the number of parameters to be determined, *i.e.* if the quantitative validity of the polynomial expression may be looked upon as a rule, we know how to interpret deviations from this rule. Discrepancies then provide valuable chemical information, *e.g.* concerning association, dimerization, specific interaction between particular ligands in neighboring positions, *etc.* Since our expression refers to all classes of molecules with ligands at the corners of a tetrahedron having symmetry D_{2d}, a comparison of ligand parameters for classes with different skeletons, such as the derivatives of spiranes, of biphenyl, of biazulene, *etc.* should prove interesting regarding the special role played by the particular skeleton. Deviations from D_{2d}-symmetry due to twisting of two parts of the skeleton into the symmetry D_2, as *e.g.* in the case of the biphenyl derivatives, should then be recognizable in the form of additive contributions to the optical activity. These contributions can be investigated by suitable experimental means. The principle is similar to that discussed here for the separate measurement of the λ- and μ-components.

The number of different pairs of enantiomers $Z_p(\rho)$ fundamentally possible for ρ different kinds of ligands shows the heuristic value of the expression (3). The determination of parameters λ(l) and μ(l) is necessary only up to a common additive constant, since both polynomials depend only on differences in the values of the parameters. Therefore we choose the values of the parameters for hydrogen to be zero, *i.e.* $\lambda(H)=\mu(H)=0$. The numbers $Z_p(\rho)$ of different enantiomeric pairs of chiral molecules which can be built up with altogether ρ kinds of ligands follow from general formulas derived in ref.[5].

$$Z_p(\rho)=\tfrac{1}{8}\rho(\rho-1)\{(\rho-2)(\rho+1)+4\}$$

Table 1.

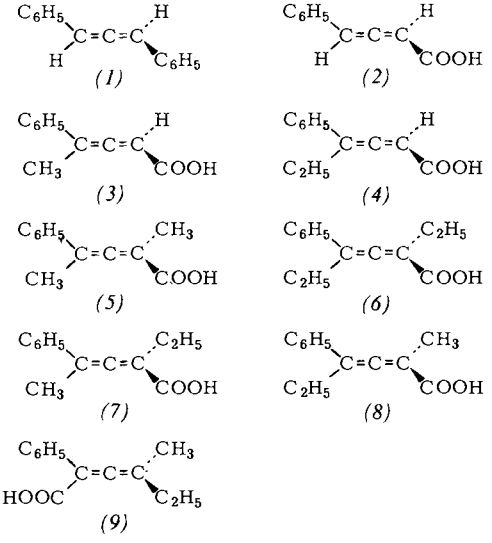
ρ	1	2	3	4	5	6	10
$Z_p(\rho)$	0	1	6	21	55	130	1035

Table 1 shows a number of examples illustrating the formula and gives some idea of the heuristic value of a semiempirical procedure using the λ-polynomial.

2. Experimental Test

The experimental test requires a number of optically pure derivatives not related to one another as enantiomers. This number should be greater than the number of kinds of ligands that occur. Many optically active allenes are described in the literature. In most cases the compounds have not been completely resolved into their antipodes or their optical purity is unknown. Therefore it was necessary to synthesize new compounds and resolve them into enantiomers for the above purpose.

It was found to be experimentally advantageous and theoretically permissible to restrict the test initially to the ligands H, CH_3, C_2H_5, C_6H_5, and COOH and investigate the compounds *(1)–(9)*, or their enantiomers.



The molecular rotations of the optically pure allene derivatives *(1)*[6] and *(2)* to *(4)*[7] were known. We synthesized the other compounds and resolved *(5)–(8)* into the antipodes[8]. Resolution was not achieved in the case of *(9)*, despite repeated attempts.

For this reason it has not yet been possible to perform a direct measurement of the μ-component by observing the optical rotation of the mixture composed of the compounds *(7)*, *(8)*, and *(9)*. Therefore we have used measurements on chiral derivatives with pairs of like ligands knowing that the μ-component vanishes in this case. Compounds of this type, *(1)*, *(2)*, *(5)*, and *(6)* allow us to determine ε_1- and the λ-values of all the ligands occurring pounds are calculated with these values on the assumption that the μ-component makes no noticeable contribution. Because this description works we have an indirect proof of the smallness of the μ-component.

For the test, conditions for measuring the molecular rotations must be as similar as possible. To rule out the influence of dissociation, association, and possible solvation, especially for carboxylic acids, the measurements were carried out in solutions of approximately equal concentration in ethanol. Rotation values for the compound *(1)* in ethanol and compound *(2)* in methanol were available

from the literature. The rotation for *(2)* was converted into the value for ethanol with the aid of the Lorentz factor $(n^2+2)/3$. Though this correction is problematic, it is small and therefore not critical. Tables 2–6 give rotation values for solutions in ethanol which are marked with an asterisk (*) if they were not measured in this solvent but calculated from the values found in methanol with the aid of the correction mentioned. The rotations are for the sodium D line ($\lambda = 589$ nm).

It was established by chemical degradation for the compounds *(2)*, *(3)*, and *(4)*[7] and shown by kinetic resolution of the racemate for the previously[10] partly resolved compounds *(5)* and *(8)* to be probable that the components with positive rotation have the (*S*) configurations as indicated in the formulas. The dextrorotatory compound *(1)* also has this configuration[9]. Therefore it may be assumed that the configurations indicated give a positive rotation for the similar derivatives *(6)* and *(7)*. We have confirmed this by comparison with circular dichroism spectra[8].

3. Results and Discussion

The second column in Table 2 shows the experimentally determined values of the molecular rotation $[\Phi]_D^{25}$. These give $\varepsilon_1 = 1$ and with $\lambda(H) = 0$ the values of the parameters $\lambda(C_6H_5)$, $\lambda(COOH)$, $\lambda(CH_3)$, and $\lambda(C_2H_5)$. The molecular rotations as described by the λ-polynomial are listed in the third column. It should be noted that discrepancies between corresponding numbers in the second and third column are only due to the parameter values having been rounded off.

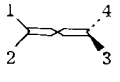
Table 2. Measured and calculated [eq. (4)] optical rotation of allene derivatives having the (*S*) configuration.

Cpd.	$[\Phi]_D^{25}$	χ
(1)	+1958	+1960
(2)	+ 686*	+ 682
(5)	+ 280	+ 282
(6)	+ 88.8	+ 89

$\lambda(H) = 0$
$\lambda(C_6H_5) = +44.3$
$\lambda(COOH) = +15.4$
$\lambda(CH_3) = +7.7$
$\lambda(C_2H_5) = +12.6$

Table 3 similarly shows experimental and theoretical rotation values now calculated from known parameter values according to Table 2 for the compounds *(3)*, *(4)*, *(7)*, and *(8)*. The deviation for *(4)* is little more than that corresponding to the experimental error. Therefore at least for the allenecarboxylic acids we may say that for practical purposes the μ-component vanishes and that the shortened expression

$$\chi(l_1, l_2, l_3, l_4) = [\lambda(l_1) - \lambda(l_2)][\lambda(l_3) - \lambda(l_4)] \qquad (4a)$$



is sufficient for the calculation of rotation angles.

Table 3. Measured and calculated [eq. (4a)] optical rotation of allene derivatives having the (*S*) configuration.

Cpd.	$[\Phi]_D^{25}$	χ
(3)	+565*	+564
(4)	+537*	+488
(7)	+103	+102
(8)	+253	+244

The algebraic theory mentioned in Section 1, the starting point for our analysis, yields the polynomial as an approximation for the optimum chirality function depending on two parameters λ and μ. The approximation is based on the assumption that for "similar" ligands the general expression in ligand-specific parameters can be terminated with the first non-vanishing term in a series expansion in these parameters. Without this approximation the qualitatively complete function could be written as a linear combination of the two components of formula (3), the coefficients being totally symmetrical functions in the corresponding parameters. Thus the approximation is justified by the assumption that with a suitable choice of these parameters, *i.e.* with a suitable concept of similarity, the totally symmetrical factors become practically constant and can be expressed by correspondingly changed λ- and μ-values, the coefficients simplifying themselves to the factors $\varepsilon_1 = \pm 1$ and $\varepsilon_2 = \pm 1$.

From a semiempirical point of view there is no reason to prefer the molar rotation; it may well be possible to obtain good results with the specific rotation. Naturally the parameters must then be redetermined. A test exactly similar to that described above for the specific rotation is illustrated in Tables 4 and 5.

Table 4. Measured and calculated specific rotation of allene derivatives having the (*S*) configuration.

Cpd.	$[\alpha]_D^{25}$	χ
(1)	+1020	+1018
(2)	+ 428*	+ 421
(5)	+ 149	+ 148
(6)	+ 41	+ 41

$\lambda'(H) = 0$
$\lambda'(C_6H_5) = +31.9$
$\lambda'(COOH) = +13.2$
$\lambda'(CH_3) = +7.2$
$\lambda'(C_2H_5) = +11.2$

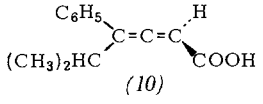
Table 5. Measured and calculated specific rotation of allene derivatives having the (*S*) configuration.

Cpd.	$[\alpha]_D^{25}$	χ
(3)	+ 324*	+ 326
(4)	+ 286*	+ 273
(7)	+ 51	+ 49
(8)	+ 125	+ 124

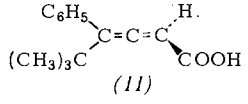
The data available are insufficient to permit a decision between the degree of approximation for molar and speci-

fic rotation. The agreement in both cases is surprisingly good. We regard this as sufficient reason on the one hand for further experiments and on the other for a quantum-mechanical treatment with the aim of correlating the parameter values with physical quantities and of getting a more precise concept of the degree of accuracy.

The experimental (molecular) rotations of compounds *(10)* and *(11)*[7], corrected for ethanol as the solvent, are used to determine further parameters (Table 6).



(10)



(11)

Table 6. Measured optical rotation of allene derivatives having the (*S*) configuration.

Cpd.	$[\Phi]_D^{25}$
(10)	+422*
(11)	+390*

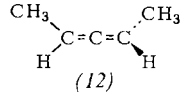
$\lambda((CH_3)_2CH) = +16.9$
$\lambda((CH_3)_3C) = +18.9$

Table 7 shows a comparison of the measured molecular rotations in various solvents for the partly resolved allene derivatives *(12)–(16)* and those which are calculated by using the λ-polynomial for the component present in excess and related to ethanol as the solvent. The components present in excess have the configurations shown in the extended formulas.

Table 7. Measured and calculated optical rotation of mixtures of enantiomers and of the pure predominant component.

Cpd.	Ref.	Solvent	$[\Phi]_D^{25}$	χ
(12)	[6]	CCl_4	− 17.2	− 59
(12)	[12, 13]	$(C_2H_5)_2O$	− 10.4	− 59
(13)	[6]	CCl_4	+ 10.7	+159
(14)	[14]	C_6H_6	−110[a]	−357
(15)	[11]	C_2H_5OH	−133	−237
(16)	[15]	not given	− 45.4	− 76

[a] $[\Phi]_{578}^{25}$ was measured.



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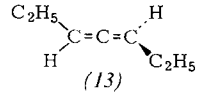

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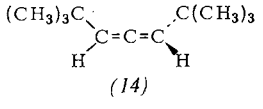

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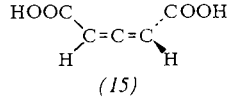

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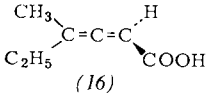

(16)

Since resolution of the racemate is often incomplete and the degree of resolution generally difficult to assess, the semiempirical aspect of our theory becomes particularly important due to the present test on the allenes. If the ligand parameters are known, one may calculate the degree of resolution from the measured rotation without experimental knowledge of the optical activity of the pure compounds, and determine the configuration of the component present in excess. Table 7 accordingly gives an idea of the optical purity of the compounds listed.

Only for molecular classes belonging to category "a" as defined below can a subclassification distinguishing heterochiral molecules be given which is free from arbitrary definitions and exclusively based on chiral properties. Consequently a nomenclature using the concepts "right" and "left" can be used to denote chirality properties of molecules even if they are neither identical nor enantiomeric.

With regard to classes of category "a" this classification has been to correspond to the sign of the chirality polynomial of lowest degree. The sign, on the other hand, is determined by the sequences of the λ-values for the ligands according to the distribution at the skeleton sites with a given numbering.

Generally a class with two skeleton sites belongs to category "a" or for $n>2$ if and only if the skeleton has mirror planes each containing $n-2$ sites.

In the case of allene derivatives the skeleton has four sites and two mirror planes each containing two sites, which shows that the above conditions for category "a" are fulfilled. We may conclude from our experiments that the polynomial predicts the correct sign of optical rotation insofar as the experimentally established λ-values are used and the rotation angle is not extremely small. Therefore we may relate the signs of rotation angles to a classification according to (R_λ)- and (S_λ)-configurations referring to the λ-values instead of those used by *Cahn, Ingold,* and *Prelog*[17] and propose two theorems which should apply if the rotation angle is not very small.

1. 1,3-Disubstituted allenes with substituents whose λ-values are greater than zero lead to positive rotation angles if (S_λ)-configurated, and to negative angles if (R_λ)-configurated.

2. Optically active allene derivatives having two pairs of like ligands, *i.e.* derivatives having the symmetry C_2, lead to positive rotation angles if (S_λ)-configurated, and to negative angles if (R_λ)-configurated.

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The Stereoselective Acylation of Racemic Secondary Alcohols with Phenyltrifluoromethylketene as an Experimental Test of the Stereochemical Analogy Model

By Ernst Anders, Ernst Ruch, and Ivar Ugi [*]

Validity of the stereochemical analogy model[1,2] for stereoselective reactions is tested on acylations of racemic chiral secondary alcohols with phenyltrifluoromethylketene. The product ratios for the diastereomeric esters formed can be calculated using a formula derived from the general model for the special case, the results agreeing with the experimental data within the accuracy of the measuring method (integration of the ^{19}F-NMR signals).

1. Theoretical

Stereoselective reactions are chemical reactions that lead exclusively or preferentially to one of several possible or conceivable stereoisomeric products. From the standpoint of their theoretical treatment stereoselective reactions can be divided into two categories.

One category is characterized by the fact that obvious physical or geometrical features indicate the direction of the selection. The simplest example of this is strong steric hindrance for some reaction products. Less obvious, but still capable of being discussed in conventional terms, are cases in which a decision is provided by the answer to the question whether a geometric rearrangement with continuous change of the electron system proceeds *via* transition complexes with bonding or antibonding states. The application of symmetry criteria to the bonding orbital system or qualitative aspects of a quantum-mechanical calculation are sufficient in such cases. Contributions to this topic have been made by various authors, examples being quantum-mechanical investigations by *Fukui*[3], *van der Lugt* and *Oosterhoff*[4], *Van der Hart, Mulder,* and *Oosterhoff*[5], and *Dewar*[6], as well as rules that can be justified by such analyses, such as the Woodward-Hoffmann rules[7].

The second category cannot be treated by these methods. It comprises reactions characterized by the absence of qualitative differences in bonding of competing situations. It includes *e.g.* asymmetrically induced syntheses, reactions in which the inducing part, the chiral reference system, of a reacting molecule does not participate directly in the reaction. *Cram*[8] and *Prelog*[9] have proposed empirical rules for direction of the stereoselectivity of certain types of asymmetrically induced reactions.

In the absence of qualitative differences in the bonding behavior for stereoisomeric products or transition complexes, predictions concerning the stereoselectivity of reactions of the second category can be based on the analogy of eigenstates. This analogy can be stated mathematically and has consequences that can be tested experimentally. States of stereoisomers may be considered analogous if they correspond to electron distributions and motion of the atomic nuclei, but belong to molecules which differ by ligand permutations on a common molecular skeleton. Thus analogous states represent geometrically different but energetically similar situations. Since most states, with the possible exception of those with very high energies, can be classified in this manner, the free enthalpy of formation of a stereoisomeric species is substantially determined by a molecular skeleton, its bonds with ligands, and the nature of the ligands. Contributions due to the mutual interaction of the ligands are relatively small. The free enthalpies of various stereoisomeric species are thus functions of the properties of the ligands, and may be permuted, or may remain unchanged on constitution-preserving permutations of the ligands, depending on whether the ligand permutation corresponds to a change of configurations or merely conformational interconversions within the same species. These functions may be regarded as a basis for a representation of the group of constitution-preserving permutations. The situation just outlined is stated *per definitionem*

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in the "stereochemical analogy model"[1]; in any particular case its validity depends on how well the states can be classified according to the analogy discussed.

The model allows conclusions regarding the stereoselectivity of the thermodynamic equilibrium of stereoisomeric products, and applies also to kinetically controlled reactions if stereoisomeric transition complexes in thermodynamic equilibrium can be conclusively assigned to the products. In both cases we have "corresponding reactions". In corresponding reactions the logarithms of the concentration ratios of the reaction products and their free enthalpies, or the free enthalpies of the corresponding transition complexes, are a basis for the representation of the group of constitution-preserving permutations. The model is useful in connection with classes of reactions that differ in the set of ligands attached to a molecular skeleton which is characteristic of the class. Depending on the geometry of the skeleton, we obtain a certain transformation behavior with regard to constitution-preserving permutations for the logarithms of concentration ratios of stereoisomeric reaction products or for the logarithms of products of such ratios. One can verify that it is reasonable according to our conditions to approximate these logarithms by mathematically simple functions of ligand-specific parameters with an appropriate transformation behavior. An empirical determination of these parameters then allows the calculation of the stereoselectivity with the aid of such expressions.

The "stereochemical analogy model" was proposed in 1966[1], and was discussed in greater detail later[2]. It refers to corresponding reactions, but also allows the treatment of complex kinetic systems that can be resolved into steps of corresponding reactions (cf.[2], p. 103).

In this paper we shall be particularly concerned with a class of asymmetrically induced syntheses, by which two diastereomeric products are formed in different quantities because of the inducing effect of a center of chirality (cf. reaction scheme I). In reactions of this type, three ligands of the inducing center (L_i, L_j, L_k) do not participate in the reaction, whereas a new center of asymmetry is formed at the fourth ligand. Accordingly, the ratio of the products depends on the nature of the three non-participating ligands L_i, L_j, L_k and their relative positions on the inducing center. The reaction products in this class of reactions are thus characterized by the configurational characteristics of the induced center, and the logarithm of their ratio $\ln c_R/c_S$ is a function of the nature of the ligands L_i, L_j, L_k and of their distribution, and this function has certain transformation properties with regard to permutations of the ligands. The function is invariant towards even permutations, assuming free rotation about the σ bond to the fourth ligand, and its sign is changed by odd permutations, since the free energy values of the transition complexes leading to the (*R*) and to the (*S*) configuration, respectively, are interchanged. We approximate this function with a polynomial of ligand-specific parameters $\lambda(L_i)$ that satisfies the transformation condition mentioned and is of the lowest order in these parameters. We obtain a chirality product, a polynomial that vanishes only if the inducing center carries two similar ligands (ligands having the same parameter value) and accordingly the stereoselectivity of the reaction vanishes.

We assign numbers to the skeletal sites on the inducing center as shown in (*A*), obtaining the formula (1).

(*A*)

$$\ln \frac{c_R}{c_S} = \rho(\lambda_1(L_i)-\lambda_2(L_j))(\lambda_2(L_j)-\lambda_3(L_k))(\lambda_3(L_k)-\lambda_1(L_i)) \quad (1)$$

The subscript of λ refers here to the position numbers. ρ is a reaction parameter that is assumed to be constant for reactions of the same class and similar reaction conditions. On the other hand

$$\ln \frac{c_R}{c_S} = -(G_R^* - G_S^*)/RT \quad (2)$$

where G_R^* and G_S^* are the free enthalpies of the transition complexes.

In eq. (1), reference can be made to the configuration on the inducing center with the aid of a nomenclature factor δ if the fourth ligand on the inducing center, *i.e.* the ligand participating in the reaction, retains in all reactions its relative, sequential priority according to the Cahn-Ingold-Prelog convention[22]. This condition is satisfied in our experiments (Section 2). Eq. (1) can thus be written in the form (1 a):

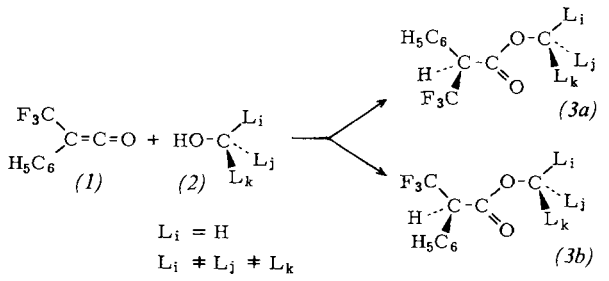
$$\delta \ln \frac{c_{RR}}{c_{SR}} = \rho(\lambda_1(L_i)-\lambda_2(L_j))(\lambda_2(L_j)-\lambda_3(L_k))(\lambda_3(L_k)-\lambda_1(L_i)) \quad (1\,a)$$

where $\delta = +1$ for the (*R*) configuration of the inducing center and $\delta = -1$ for the (*S*) configuration. In the stereochemical analogy model, eq. (1) or (1 a) is a special form for a particular case. It may be interpreted as the first term of a Taylor series and also as the first term of an orthogonal polynomial expansion for a function with the required symmetry behavior[10, 11]. Other expressions, such as that based on the second approximation method[12], are possible, but are not discussed in this article.

Experimental data given by *Prelog et al.* for syntheses of the type described[13, 14] were used by *Prelog* only to confirm a qualitative rule. Though the quantitative evaluation of these data does not lead to conflict with our theory[2], we felt it necessary to test the validity of the stereochemical analogy model in the special form (1 a) by a reliable and sufficiently accurate set of measurements based upon a type of reaction that can be expected to yield quantitatively reliable data under suitably chosen conditions.

2. Experimental

The asymmetric acylation of chiral secondary alcohols *(2)* with phenyltrifluoromethylketene *(1)* (Scheme I) was chosen as the model reaction.



Scheme I.

In this reaction, the tricoordinate carbon atom of the ketene group is converted into a tetracoordinate center of chirality which has the (*S*) configuration in the ester *(3a)* and the (*R*) configuration in *(3b)*. The reasons for choosing this reaction type were the following:

Investigations by *Pracejus*[15,16] demonstrate that the stereoselective addition of 1-phenylethylamine to phenylmethylketene in suitable solvents is exclusively kinetically controlled over a wide temperature range. The description of the experiments[16] contains clear evidence that the competing reactions leading to the two diastereomeric products are a pair of corresponding reactions. Accordingly, the asymmetric acylation of secondary alcohols of the type *(2)* with similar ketenes should also have these properties. There are two types of experimental evidence indicating that reactions such as that in Schema I proceed by a pair of corresponding reactions. In the case of corresponding reactions, the concentration ratio of the products *(a)* and *(3b)* does not depend on the concentrations of the starting compounds *(1)* and *(2)*, and the logarithm of the concentration ratio (log *Q*) is a linear function of the inverse absolute temperature. Therefore, the temperature dependence of the addition of 1-phenylethanol to *(1)* was investigated between -61 and $+25$ °C as a model reaction for Scheme I. It was found that in toluene the reaction does not exhibit the required temperature dependence, whereas the linear relation was observed in methylene chloride (see Fig. 1). In both solvents the concentration ratio of the end products is independent of the initial concentrations of the reactants. It may therefore be inferred that the stereochemical analogy model, and hence also eq. (1), is valid for kinetically controlled reactions corresponding to Scheme I in methylene chloride.

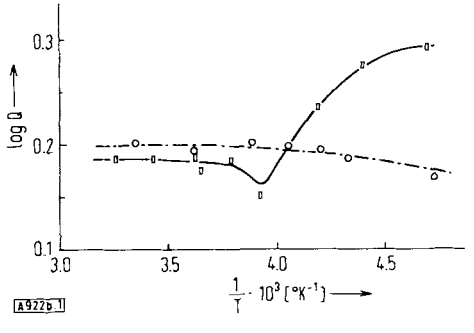
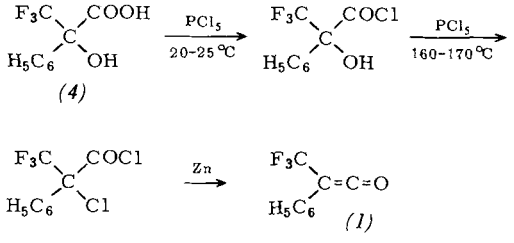


Fig. 1. Temperature dependence of the product ratio in the reaction of phenyltrifluoromethylketene with 1-phenylethanol: —— in toluene; in methylene chloride.

To test eq. (1), the number of reactions of type I investigated must be greater than the number of different ligands of the inducing chirality center. Adding the same number to all the parameter values does not affect the value of the polynomial, and multiplication by a common factor can be compensated by the reaction parameters. Thence two λ values can be chosen arbitrarily. With the λ value for hydrogen = zero ($\lambda(H) = 0$) and that for the methyl group = one ($\lambda(Me) = 1$), we have (together with ρ) one parameter less to determine than the number of ligand types occurring in the secondary alcohols *(2)* in the reactions investigated. The number of possible constitutionally different alcohols that can be derived from a set of ligands $\{L_1, L_2, \ldots, L_N\}$ is $\binom{N}{3}$. With increasing N, the number of data that can be calculated increases steeper than the number of measurements required for the determination of the parameters.

We have investigated twelve reactions, whose calculation requires six parameters.

Phenyltrifluoromethylketene *(1)* was prepared as indicated in Scheme II from α-trifluoromethylmandelic acid *(4)*. The latter has been described by *Mosher et al.*[17].



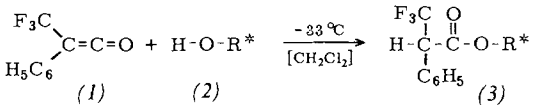
Scheme II.

The alcohols *(2)* with the ligands L_i, L_j, L_k = H, CH_3 (Me), C_2H_5 (Et), $CH(CH_3)_2$ (iPr), $C(CH_3)_3$ (tBu), C_6H_5 (Ph), 2,4,6-$(CH_3)_3C_6H_2$ (Mes) were prepared by known methods[18] and were reacted with the ketene *(1)* under standard conditions (0.09 M *(1)*, 1.1 M *(2)*; -33 ± 2 °C; in CH_2Cl_2) in accordance with Scheme I. The product ratio of *(3a)* to *(3b)* was determined by ^{19}F-NMR; this ratio can be measured sufficiently accurately with trifluoroacetic acid as an *external*[*] standard[19]. Since the signals of the two diastereotopic[20] trifluoromethyl groups are not affected appreciably by the ^{1}H signals of the other parts of the molecule of *(3)* or by small quantities of impurities, the analysis can be carried out on crude ester mixtures *(3)*.

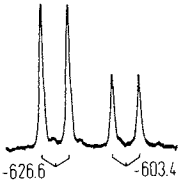
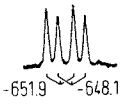
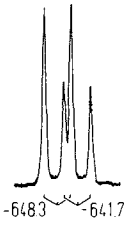
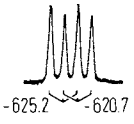
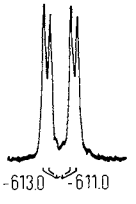
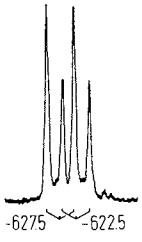
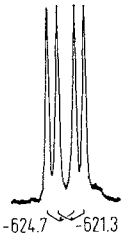
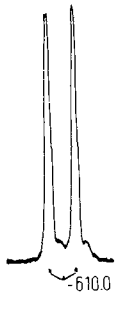
In two cases the configuration of the carboxylic acid moiety of the preferentially formed ester *(3)* was determined on a sample which was obtained by acylation of optically pure alcohol *(2)* [(*S*)-(−)-1-phenylethanol and (*S*)-(+)-1-*tert*-butylethanol]. Each of the resulting ester mixtures was then hydrolyzed with acid and the optical rotations of the resulting α-trifluoromethylphenylacetic acid were measured. The results show that (*R*,*S*) diastereomers are preferentially formed in both cases. The NMR-spectroscopic

[*] As an *internal* standard, trifluoroacetic acid can increase the difference in the chemical shifts of diastereotopic trifluoromethyl groups [19], but it may also affect the ratio of the quantities of diastereomeric esters.

Table 1. Results of checking the validity of a special formula (1a) arising from the stereochemical analogy model for the special case (Scheme I).



(1) (2) (3)

R*	^{19}F-NMR	% (R, S)–(3) c_{exp}	% (R, S)–(3) c_{calc}	R*	^{19}F-NMR	% (R, S)–(3) c_{exp}	% (R, S)–(3) c_{calc}
Mes -C-Me H *(a)*		68	67.3	Mes -C-iPr H *(g)*		56	67.3
Mes -C-Et H *(b)*		66	67.3	tBu -C-iPr H *(h)*		54	54.0
Ph -C-iPr H *(c)*		64	62.0	tBu -C-Et H *(i)*		53	54.0
Ph -C-Me H *(d)*		61	62.0	iPr -C-Et H *(j)*		52	50.0
Ph -C-Et H *(e)*		61	62.0	iPr -C-Me H *(k)*		50	50.0
tBu -C-Me H *(f)*		55	54.0	Et -C-Me H *(l)*		50	50.0

studies show that the doublet signal of the trifluoromethyl group of the preferentially formed product appears at a lower field than the corresponding doublet of the other component. A similar result was obtained by *Mosher et al.*[21] in a different context. On attempting to synthesize the optically pure (*S*,*R*) ester from optically pure starting compounds (acyl chloride of (*S*)-(+)-α-trifluoromethylphenylacetic acid and (*R*)-(+)-phenyl-*tert*-butylmethanol), as a result of partial diastereoisomerization we obtained an ester mixture, which was reduced with $Li[AlH_4]$ for configurational assignment.

The preferentially formed diastereoisomer in this reaction, as in the reactions in accordance with Scheme I, has the (*R*,*S*) configuration, and its ^{19}F doublet appears at a lower field than that of the other component. Racemic alcohols *(2)* can therefore be reacted according to Scheme I, and the stereoselectivity of the reaction determined by ^{19}F-NMR analysis.

The results of our investigations are summarized in Table 1. c_{exp} is the experimentally determined percentage of the (*R*,*S*) component in the ester mixture. The values of the parameters that were used to calculate the percentage of the (*R*,*S*) components (c_{calc}) were:

$\lambda(H) = 0.00$, $\lambda(Me) = 1.00$ } *per definitionem*
$\lambda(Et) = 1.00$
$\lambda(iPr) = 1.00$
$\lambda(tBu) = 1.25$
$\lambda(Ph) = 1.60$
$\lambda(Mes) = 1.79$
$\rho = 0.512$

Except in the case of reaction (g), these calculated values are found to agree with the experimental percentages to within the accuracy of the integration of the ^{19}F-NMR signals (approx. ± 3 to ± 5%).

The deviation in reaction (g) (mesitylisopropylmethanol) is presumably due to racemization of the ester, which is also observed in the corresponding reaction product of *Mosher et al.* The assumption of a side reaction or of a further reaction that leads to a decrease in the stereoselectivity is also supported by the direction of the deviation from the theoretical value. The calculation using the λ values confirmed by experiments (j) and (k) (λ(iPr) = λ(Me) = λ(Et)) gives too high a stereoselectivity for *(3g)*.

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Semiempirical Use of Chirality Functions[1,3] for the Description of the Optical Activity of Methane Derivatives in the Transparent Region

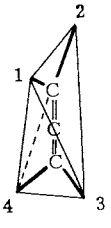
By Wolf Jürgen Richter, Bernd Richter, and Ernst Ruch[*]

The optical activity can provide detailed information about the configuration and conformation of methane derivatives if the chirality function is resolved, according to the theory of chirality functions[3] and the quantum mechanical theory of the optical activity of methane derivatives[4], into its components which are compared with experimental data. A first step in this direction is undertaken in the present article and it will be shown that the second approximation method for determining the conformationally independent contribution to the optical activity yields quantitatively good results. Description of the overall optical rotation by this component is expectedly poor where interactions between ligands, *e.g.* hydrogen bonding, tend to favor specific conformations. A quantitative understanding of such additional effects appears promising in conjunction with analyses of the kind described.

1. Theoretical

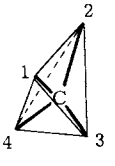
The semiempirical use of chirality functions based on the polynomial method[1,3] has been tested experimentally in the special case of the optical activity of allene derivatives. From the good results achieved[2], we draw the justification for attempting the same test in the case of the more complicated class of methane derivatives. Though the polynomials and the expressions based on a so-called second method[1,3] each correspond to the same mathematical approximation principle for different classes of molecules, the various classes show characteristic differences in the heuristic value of such a procedure, the mathematical effort, the amount of experimental information required, and the accuracy of the approximation. It is therefore appropriate to begin with a comparative outline of the problems arising in an analysis of the optical activity of allene and of methane derivatives from the theoretical point of view and from the standpoint of experimental verification.

The concept "class of molecules", on which the general theory of chirality functions[3] is based, involves an idealization necessary for a proper formulation of class-specific influences upon a pseudoscalar observation like the optical activity for all molecules of a given class. In the case of methane derivatives this idealized situation is the following: The central tetracoordinate carbon with its bond directions is regarded as a molecular skeleton of symmetry T_d. The C_{3v}-symmetry axes coinciding with a bond direction define the symmetry of the corresponding ligands. Therefore the ligand symmetry must be C_{3nv} where $n \geq 1$ or $C_{\infty v}$ if the ligands are rigidly fixed, or $C_{nv}, n \geq 1$, or $C_{\infty v}$ if they exhibit free rotation. Inasmuch as methane derivatives fulfill this condition we call them T_d-derivatives. Allene derivatives with the skeletal symmetry D_{2d} and with ligands having the subsymmetry C_s of D_{2d} referring to the ligand sites may be called D_{2d}-derivatives. Whereas a quantitatively complete chirality function of D_{2d}-derivatives contains two components which may be designated as D_{2d} and T_d-components, T_d-derivatives contain only the T_d-component. This statement applies also to all quantitatively complete approximative descriptions for optical rotation, *e.g.* to expressions corresponding to the first and to the second method mentioned above.



$$\chi(l_1,l_2,l_3,l_4) = \varepsilon_1[\lambda(l_1)-\lambda(l_2)][\lambda(l_3)-\lambda(l_4)] + \varepsilon_2[\mu(l_1)-\mu(l_2)][\mu(l_1)-\mu(l_3)][\mu(l_1)-\mu(l_4)] \times [\mu(l_2)-\mu(l_3)][\mu(l_2)-\mu(l_4)][\mu(l_3)-\mu(l_4)] \quad (1a)$$

$$\tilde{\chi}(l_1,l_2,l_3,l_4) = \varphi_1(l_1,l_3)+\varphi_1(l_2,l_4)-\varphi_1(l_1,l_4)-\varphi_1(l_2,l_3) + \varphi_2(l_1,l_2,l_3)-\varphi_2(l_2,l_3,l_4) + \varphi_2(l_3,l_4,l_1)-\varphi_2(l_4,l_1,l_2) \quad (1b)$$



$$\chi(l_1,l_2,l_3,l_4) = \varepsilon[\mu(l_1)-\mu(l_2)][\mu(l_1)-\mu(l_3)][\mu(l_1)-\mu(l_4)] \times [\mu(l_2)-\mu(l_3)][\mu(l_2)-\mu(l_4)][\mu(l_3)-\mu(l_4)] \quad (2a)$$

$$\tilde{\chi}(l_1,l_2,l_3,l_4) = \varphi(l_1,l_2,l_3)-\varphi(l_2,l_3,l_4)+\varphi(l_3,l_4,l_1)-\varphi(l_4,l_1,l_2)$$

where (2b)

$$\varphi(l_1,l_2,l_3) = \varphi(l_2,l_3,l_1) = \varphi(l_3,l_1,l_2) = -\varphi(l_1,l_3,l_2) = -\varphi(l_3,l_2,l_1) = -\varphi(l_2,l_1,l_3)$$

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In formula (2a), $\mu(l_i)$ is a real ligand-specific parameter for the ligand l in the bond direction of the tetrahedral skeleton denoted by *i*. The value of the factor ε is either $+1$ or -1 for the entire class of T_d-derivatives, which as $\mu(l)$ must be determined empirically. $\varphi(l_i,l_j,l_k)$ in formula (2b), a function of the three ligands l_i, l_j and l_k in positions 1, 2, and 3, changes its sign on odd permutations of the ligands and is the empirical determinative element of the second method.

The experimental data for allene derivatives in[2] could be explained by neglecting the T_d-component. That means that well-defined contributions to the optical rotation which are in principle non-vanishing and can be separated by experimental means and measured, are negligibly small in the case of allene derivatives. The problem of the relevance of various components does not arise in the case of T_d-derivatives but it becomes significant for methane derivatives not subject to the T_d-condition. Apart from the difficulty of finding derivatives which satisfy the T_d-condition, at least approximately, there is the problem of establishing whether the T_d-component can be described precisely enough by one or both of the two approximative Ansätze. In the case of allene derivatives the λ-polynomial turned out to be perfectly satisfactory[2]. In the case of methane derivatives we shall approach this question first by referring to the results of a quantum-mechanical theory for this class.

A quantum-mechanical treatment of the optical activity of methane derivatives has been explicitly carried out up to the second order of perturbation defined as the interaction between ligands[4]. Apart from the assumption of fixed atomic nuclei, the model used contains no further serious simplifications. In this theory the T_d-component appears as a part of the second order correction, whereas contributions to the optical activity due to deviations from the T_d-condition are already described by corrections of the zeroth or first order. They vanish therefore for T_d-derivatives. The quantum-mechanical form of the T_d-component coincides exactly with Ansatz (2b). The polynomial on the other hand, generally a simplifying specialization of the expression based on the second method, can be obtained from the quantum-mechanical expression only with drastic simplifications. The parameters are correlated here with "representative lengths" corresponding very roughly to the distances between the central carbon and the positive charge centers of the ligands. A reasonably acceptable description by means of the polynomial, therefore, can be expected only for derivatives of a special selection, which cannot be specified *a priori*.

However, despite the superiority of Ansatz (2b), Ansatz (2a) is still of interest. Like the D_{2d}-derivatives of allene, the methane derivatives corresponding to the T_d-condition belong to the very few classes where it is possible in principle to give a classification of configurations according to "left" and "right" and referring exclusively to chirality and not to some further arbitrary definitions[5]. The principle for this differentiation is provided by the sign of the polynomial. If we assign different values of the parameter to different types of ligands, the polynomial (2a) becomes zero if and only if the molecule described is achiral. As far as the polynomial can be used to describe the optical rotation, at least to predict the sign, the sign of the optical rotation simultaneously gives a classification of configurations and this classification refers to the sequence of the parameter values for ligands according to their fixation on numbered sites of the skeleton. This seems to work for the allene derivatives investigated in ref.[2] and it would be worth stating if it should also apply in the case of methane derivatives, even if the polynomial does not give the amount of the optical rotation in a satisfactory manner.

2. Test Method

In order to determine the optical rotation of different $\binom{N}{4}$ pairs of enantiomers which can be built up with N different types of ligands, we need experimental data for the determination of $N-1$ parameters and of ε if we are concerned with the polynomial. If concerned with the second method, we need at least $\binom{N-1}{3}$ experimental optical rotation values. The above discussion suggests the following steps for an experimental test.

1. Since formula (2b) may be considered as the result of a second order perturbation quantum-mechanical treatment as far as T_d-derivatives are concerned, we test this expression for those derivatives or use it as a criterion of whether the T_d-condition is satisfied sufficiently well.

2. Appreciable deviations of the optical rotation from the theoretical values according to expression (2b) are attributed to a deviation in the geometry from the T_d-condition. We may explain such deviations as additional contributions that have to be accounted for by expressions of the first or zeroth order of perturbation according to the general formulas for methane derivatives published in ref.[4].

3. Derivatives for which expression (2b) can be confirmed are tested against the simpler expression (2a) in the hope of obtaining at least a correct description of the sign of the optical rotation for derivatives belonging to a certain subclass.

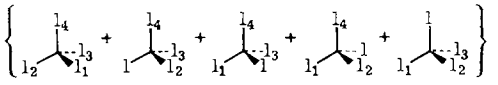
Only points 1 and 3 were examined on the basis of the experiments discussed here, since a detailed analysis according to point 2 seems sensible only after having a more detailed knowledge of the degree of approximation in the description of the rotatory power of T_d-derivatives.

For the experimental test we use a functional equation which follows from expression (2b) and does not depend on the special type of functions $\varphi(l_i,l_j,l_k)$ chosen.

$$\tilde{\chi}(l_1,l_2,l_3,l_4) = \tilde{\chi}(l,l_2,l_3,l_4) + \tilde{\chi}(l_1,l,l_3,l_4) + \tilde{\chi}(l_1,l_2,l,l_4) + \tilde{\chi}(l_1,l_2,l_3,l) \quad (3)$$

The chirality function on the left-hand side of equation (3) does not depend on the choice of the ligand l. The equation can be verified by decomposing each of the chirality functions on the right-hand side of (3) into the three-ligand functions according to (2b). Due to the sign reversal of $\varphi(l_i,l_j,l_k)$ on odd permutations of the ligands, one finally obtains the left-hand side of (3). Formula (3) leads to a very simple

experimental test for expression (2b), since it predicts a linear dependence of the measured optical rotations for various T_d-derivatives, which is specific for our expression and is not a triviality that can be verified by symmetry arguments. This statement becomes evident through the fact that the mixture

$\frac{1}{5}$  (4)

is not racemic if all the ligands are different and equation (3) leads to the zero identity (5)

$$\tilde{\chi}(l_2,l_1,l_3,l_4) + \tilde{\chi}(l,l_2,l_3,l_4) + \tilde{\chi}(l_1,l,l_3,l_4) + \tilde{\chi}(l_1,l_2,l,l_4) + \tilde{\chi}(l_1,l_2,l_3,l) \equiv 0 \quad (5)$$

for the optical rotation of such a mixture.

Of course this is a theoretical approximation for the measured angle of rotation of the mixture, but it should be a very good one as far as the T_d-condition for all the five constituting chemical compounds is fulfilled.

Experimentally accessible methane derivatives, separable into antipodes, measurable under analogous conditions, and allowing the formation of several mixtures of type (4) normally do not match the selection principle for T_d-derivatives. Therefore we have to use compounds for which the T_d-condition is not perfectly fulfilled but where it seems sensible to assume that the T_d-component contributes the main part to the optical rotatory power. We have to test this assumption by the relation (5), knowing that there are additional contributions falsifying the value zero for the mixture and knowing that even the T_d-component sums up to zero in so far as it is correctly described by formula (2b) or (2a). For this purpose we proceed as follows:

We measure the molar optical rotations $\varphi(l_i,l_j,l_k,l_s)$ of five non-enantiomeric derivatives belonging to an ensemble of type (4) and establish the experimental value $\bar{\Phi}$ of the corresponding mixture according to equation (6).

$$\bar{\Phi} = \tfrac{1}{5}\{\Phi(l_2,l_1,l_3,l_4) + \Phi(l_5,l_2,l_3,l_4) + \Phi(l_1,l_5,l_3,l_4) + \Phi(l_1,l_2,l_5,l_4) + \Phi(l_1,l_2,l_3,l_5)\} \quad (6)$$

We compare the absolute value $|\bar{\Phi}|$ with the absolute average value for a mixture of type (4) expected if there is no preferred relation like (5). If $|\bar{\Phi}|$ is found to be smaller than this average value for any mixture, except those where the T_d-condition is seriously violated for obvious chemical reasons, we may take this as an indication that a T_d-component described by (2b) is relevant and the non-vanishing value $|\bar{\Phi}|$ is mainly due to contributions from slight geometrical deviations from the T_d-condition.

The absolute value of the molar optical rotation of mixtures like (4) lies between 0 and $\bar{M}$ where $\bar{M}$ is the arithmetic mean of positive rotation angles measured on each component of the mixture or the corresponding enantiomers. The statistical mean rotation angle for the mixture (4) containing no enantiomeric compounds is then $\frac{3}{8}\bar{M}$. Therefore our criterion reads:

$$|\bar{\Phi}| < \tfrac{3}{8}\bar{M} \quad (7)$$

With increasing experimental information on mixtures of the type mentioned we arrive at a test of our assumption. Measured optical rotation angles of the pure compounds which fulfill the criterion (7) are then approximated by least-square error deviations with numbers that satisfy the zero identity (5). These numbers are taken as empirical values for an optimum function $\tilde{\chi}$ for the experimental T_d-component. With the aid of equation (3) it should be ultimately possible to make reliable predictions about the T_d-component of rotation angles that have been measured and to correlate deviations lying outside the expected degree of approximation with the T_d-deviation of the geometry in the compounds under consideration.

If relation (7) is fulfilled by a sufficient amount of experimental material, we may go further to test Ansatz (2a). With respect to expression (2a) the identity (5) can be formulated in the form of a zero identity of a determinant. If we make use of the equivalent formulation for $\chi(l_1,l_2,l_3,l_4)$ by the Vandermonde determinant (2a') we obtain (5) in the form of (5').

$$\chi(l_1,l_2,l_3,l_4) = \varepsilon \begin{vmatrix} 1 & 1 & 1 & 1 \\ \mu(l_1) & \mu(l_2) & \mu(l_3) & \mu(l_4) \\ [\mu(l_1)]^2 & [\mu(l_2)]^2 & [\mu(l_3)]^2 & [\mu(l_4)]^2 \\ [\mu(l_1)]^3 & [\mu(l_2)]^3 & [\mu(l_3)]^3 & [\mu(l_4)]^3 \end{vmatrix} \quad (2a')$$

$$\begin{vmatrix} 1 & 1 & 1 & 1 & 1 \\ 1 & 1 & 1 & 1 & 1 \\ \mu(l_1) & \mu(l_2) & \mu(l_3) & \mu(l_4) & \mu(l_5) \\ [\mu(l_1)]^2 & [\mu(l_2)]^2 & [\mu(l_3)]^2 & [\mu(l_4)]^2 & [\mu(l_5)]^2 \\ [\mu(l_1)]^3 & [\mu(l_2)]^3 & [\mu(l_3)]^3 & [\mu(l_4)]^3 & [\mu(l_5)]^3 \end{vmatrix} \equiv 0 \quad (5')$$

Numerical values satisfying condition (5) and approximating the optical rotation angles for derivatives of a mixture (4) are also values of the polynomial (2a) if certain additional relations are satisfied, as shown by *Weimann*[6].

The Newton approximation method offers a way of calculating the $\mu(l_i)$. For this purpose one uses the equations (5'')

$$\begin{vmatrix} 1 & 1 & 1 & 1 & 1 \\ [\mu(l_1)]^\nu & [\mu(l_2)]^\nu & [\mu(l_3)]^\nu & [\mu(l_4)]^\nu & [\mu(l_5)]^\nu \\ \mu(l_1) & \mu(l_2) & \mu(l_3) & \mu(l_4) & \mu(l_5) \\ [\mu(l_1)]^2 & [\mu(l_2)]^2 & [\mu(l_3)]^2 & [\mu(l_4)]^2 & [\mu(l_5)]^2 \\ [\mu(l_1)]^3 & [\mu(l_2)]^3 & [\mu(l_3)]^3 & [\mu(l_4)]^3 & [\mu(l_5)]^3 \end{vmatrix} \equiv 0 \text{ with } \nu = 0,1,2, \text{ and } 3 \quad (5'')$$

and the invariance of the polynomial χ and of the determinant (5'') toward the substitution $\mu'(l_i) = \mu(l_i) + k$ with a constant k independent of i. With $\mu'(l_1) = 0$ and the substitutions $\tilde{\chi}(l_1,l_3,l_4,l_5) = a_2$, $\tilde{\chi}(l_1,l_2,l_4,l_5) = a_3$, $\tilde{\chi}(l_2,l_1,l_3,l_5) = a_4$, $\tilde{\chi}(l_1,l_2,l_3,l_4) = a_5$ for the values of the function χ, we calculate numerical values x, y, and z from the following rapidly converging iteration equations:

$$\begin{pmatrix} x_{n+1} \\ y_{n+1} \\ z_{n+1} \end{pmatrix} = \begin{pmatrix} x_n \\ y_n \\ z_n \end{pmatrix} - \frac{1}{(x_n-y_n)(y_n-z_n)(z_n-x_n)} \begin{pmatrix} \frac{1}{a_3} y_n z_n (z_n-y_n) & \frac{1}{2a_3}(y_n^2-z_n^2) & \frac{1}{3a_3}(z_n-y_n) \\ \frac{1}{a_4} x_n z_n (x_n-z_n) & \frac{1}{2a_4}(z_n^2-x_n^2) & \frac{1}{3a_4}(x_n-z_n) \\ \frac{1}{a_5} x_n y_n (y_n-x_n) & \frac{1}{2a_5}(x_n^2-y_n^2) & \frac{1}{3a_5}(y_n-x_n) \end{pmatrix} \times \begin{pmatrix} a_3 x_n + a_4 y_n + a_5 z_n - a_2 \\ a_3 x_n^2 + a_4 y_n^2 + a_5 z_n^2 - a_2 \\ a_3 x_n^3 + a_n y_n^3 + a_5 z_n^3 - a_2 \end{pmatrix}$$

$$x = \lim_{n\to\infty} x_n,\quad y = \lim_{n\to\infty} y_n,\quad z = \lim_{n\to\infty} z_n$$

One finds the values of the parameters then from the equations:

$$\mu'(l_1) = 0$$
$$\mu'(l_2) = \left\{ \frac{a_2}{\varepsilon xyz(x-y)(x-z)(y-z)} \right\}^{\frac{1}{6}}$$
$$\mu'(l_3) = \mu'(l_2)\cdot x$$
$$\mu'(l_4) = \mu'(l_2)\cdot y$$
$$\mu'(l_5) = \mu'(l_2)\cdot z$$

Parameter values for a given ligand calculated this way from differing mixtures are naturally not the same; however, if they are not too different, it is worthwhile to seek an approximation for all the data that can be described by the expression (2b) by using the polynomial (2a) in optimum parameters. The determination of optimum values for the parameters from a large number of measurements is facilitated by the prior determination of parameter values for individual mixtures (4) by the iteration method sketched out above.

For the polynomial we must also be certain that the data are sufficient to fix the factor ε, *i.e.* only one of the two values $\varepsilon = \pm 1$ can give an acceptable approximation to the experimental data. The sign of the optical rotation for such derivatives is then determined by the sequence of the parameter values of ligands with reference to fixed numbered skeletal sites, irrespective of whether the values of the polynomial give a good approximation of the experimental data as regards absolute values.

3. Experimental

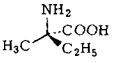
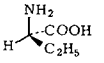
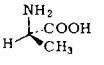
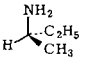
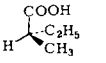
As starting materials we chose five compounds that exist as or can be derived from natural products (Table 1). Their absolute configurations have been established and their optical purity has been checked in various ways. The other 49 derivatives in Tables 2—4 were obtained by reactions in which the configuration of the products can be deduced with certainty because the central carbon is not attacked.

The reduction of the carboxyl group in the reference compounds yields alcohols of mixture *(9)* which are likewise known in optically pure form.

Esterification under mild conditions yields the ethyl esters (mixture *(13)*), which are listed together with the acids in Table 4.

The mixtures *(1)*—*(8)*, given together with mixture *(9)* in Table 2, are obtained by reactions of the amino group, leaving the four other ligands unchanged.

Table 1.

	(*R*)-Isovaline
	(*R*)-2-Aminobutyric acid
	(*R*)-Alanine
	(*R*)-2-Aminobutane (resolution of racemates, stereospecific degradation of (*R*)-2-methylbutyric acid)
	(*R*)-2-Methylbutyric acid (from fermentation amyl alcohol)

The CH_2OH groups of the compounds of mixtures *(3)* and *(8)* can be etherified with the bulky $Si(CH_3)_3$ group to obtain the derivatives in Table 3 (mixtures *(10)* and *(11)*).

The optical rotations were measured under identical conditions with plane-polarized light of the sodium D line.

The references[8-22] in Tables 2 and 4 relate only to the preparation of the compounds in question. For the preparation of all other derivatives see ref.[7].

The experimental data in Tables 2 to 4 are arranged according to mixtures of Type (4), those containing a common derivative being listed in one table. In each case the experimental values of the molar rotation $[\Phi]$ for the derivatives of the various mixtures (Na D line at 25 °C; in approx. 5% ethanolic solution, mixture *(12)* in aqueous solution) are given in the first row. The second row gives values of a function according to expression (2b) that we found as described below. Relation (7) can be assessed from the columns for $\bar{\Phi}$ and $\frac{3}{8}\tilde{M}$.

Relation (7), which is a necessary but not a sufficient condition in the individual case, gains in importance when found in agreement with known chemical facts about the T_d-condition. Therefore, derivatives whose rotation angles undoubtedly contain additional contributions due to deviations from the T_d-situation are also included in Tables 2—4. Since these additional contributions, as was mentioned, are of first or zeroth order of the perturbation treatment, they will increase rapidly with the geometrical deviation and will ultimately exceed

Table 2.

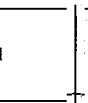
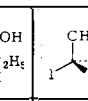
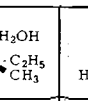
Mixture	Ligand I						$\bar{\Phi}$	$\frac{3}{8}\bar{M}$
(1)	$NH_3^+Cl^-$	−5.75[8] −4.1288	− 7.6 − 6.2428	−17.2 −15.8428	-19.5 -20.8572	+ 4.0[13] + 5.3572	−1.41	4.05
(2)	$NH_2CH_3^+Cl^-$	−5.75 −4.1288	− 9.3 − 7.8178	−20.5 −19.0178	-21.6 -23.0822	+ 6.4 + 7.8822	−1.51	4.77
(3)	$N(CH_3)_2$	−5.75 −4.1288	− 2.6 − 0.8678	− 9.8 − 8.0678	- 3.9[16] - 5.3622	+ 5.7 + 7.4322	−1.71	2.08
(4)	$NH(CH_3)_2^+Cl^-$	−5.75 −4.1288	− 4.8 − 2.9928	−24.2 −22.3928	-18.1 -19.9072	+ 7.8 + 9.6072	−1.77	4.55
(5)	$NHCH_3$	−5.75 −4.1288	− 2.88 − 1.1528	−36.2[15] −34.4728	-35.6[14] -37.3272	+ 0.7 + 2.4272	−1.706	6.08
(6)	$N(CH_3)_3^+I^-$	−5.75 −4.1288	−35.5 −30.9678	+11.5 +16.0322	- 9.8[16] - 5.2678	+19.8 +24.3322	−3.95	6.18
(7)	$N{=}CHC_6H_5$	−5.75 −4.1288	−31.0 −24.4928	+56.8 +63.3072	-71.3 -77.8072	-119.0[22] -112.4928	−5.53	21.29
(8)	NHCHO	−5.75 −4.1288	−17.0 −14.3928	+49.2[15] +51.8072	-30.0 -27.3928	− 8.5 − 5.8928	−2.41	8.28
(9)	NH_2	−5.75 −4.1288	− 3.5[11] − 1.7078	−12.77[10] −10.9778	-15.62[9] -17.4122	− 2.39[12] − 0.5978	−1.758	3.00

Table 3.

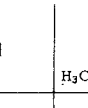
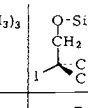
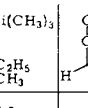
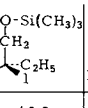
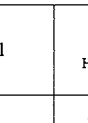
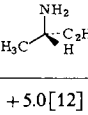
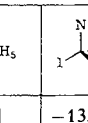
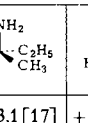
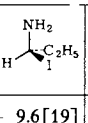
Mixture	Ligand I						$\bar{\Phi}$	$\frac{3}{8}\bar{M}$
(10)	$N(CH_3)_2$	+ 0.1 + 3.24	− 7.0 − 3.86	− 10.9 − 7.76	− 3.6 − 0.46	+ 5.7 + 8.84	− 3.14	2.05
(11)	NHCHO	+ 0.1 −14.62	−23.0 −37.72	+277.0 +262.28	−172.0 −186.72	− 8.5 −23.22	+14.72	36.04

Table 4.

Mixture	Ligand I						$\bar{\Phi}$	$\frac{3}{8}\bar{M}$
(12)	COOH	+5.0[12] +9.82	−13.1[17] − 8.28	+ 9.6[19] +14.42	−1.6[19] +3.22	−24.0[8] −19.18	−4.82	4.00
(13)	$COOC_2H_5$	+2.39[12] +5.736	−13.3[18] − 9.954	+24.8[21] +28.146	−3.12[19] +0.226	−27.5[20] −24.154	−3.346	5.33

the T_d-contribution. Large rotation angles must therefore be discussed with this reservation.

For the reasons mentioned, theoretical data on each mixture in the second row, which approximate the experimental values in the sense of the least-square error deviation with condition (5), may be regarded as possible values of a function according to expression (2b), it being noted that the validity of the relation (7) justifies this view. A combination of the aspects mentioned above leads us to an estimation of the theoretical figures if on the one hand we propose a maximum permissible value for $|\bar{\Phi}|$, *e.g.* $|\bar{\Phi}| \leq 2$, and if on the other hand we ignore those mixtures for whose derivatives marked deviations from the T_d-situation must be assumed on chemical grounds. For the cases that remain, the figures in the second row should in fact give an idea of the T_d-component.

It can be concluded from IR spectroscopic studies that the pairs of ligands NH_2/CH_2OH, $NHCHO/CH_2OH$, and $NH_2/COOH$ give rise to the formation of intramolecular or intermolecular hydrogen bonds. Some compounds of the mixture *(13)* are known to undergo considerable dimerization even at room temperature to form diketopiperazines. Bulky ligands such as $N{=}CHC_6H_5$ and $CH_2OSi(CH_3)_3$ restrict the free rotation of neighboring ligands and can thus considerably upset the T_d-situation in the time average. Compounds containing the ligand $N{=}CHC_6H_5$ are pale yellow, so that the Na D line lies at the limit of the transparent region. The dispersion ratio $\Phi_{365}/\Phi_{Na\text{-}D}$ is 3.5—6.4 here, as against 2.2—3.0 for the other compounds.

If we adopt chemical arguments of this type and the relation $|\bar{\Phi}| \leq 2$ as selection principles, we are left with the derivatives of the mixtures *(1)—(5)* as experimental material, and we shall take the data in every second row as approximate values for the T_d-components.

The attempt to approximate the function values found for expression (2b) with the polynomial (2a) shows that although the iteration method discussed earlier gives

μ-parameters by means of which the function values can be accurately described for a given mixture in several cases, common parameter values lead to a reasonable approximation only for the mixtures *(1)—(5)*. It is also found that the factor $\varepsilon = -1$ is the only possible solution for the mixtures *(1)—(5)*. With the polynomial (2a), the parameter values from the last column of Table 6 and the factor $\varepsilon = -1$, we obtain the figures in the third row of Table 5. For the sake of comparison, rows 1 and 2 again give the experimental data and the values according to expression (2b).

The parameter values found for each of the mixtures *(1)—(4)* by the iteration method and the optimum common values for all the compounds from *(1)—(5)* are shown in Table 6. From this table we obtain the following sequence:

$$\mu(H) < \mu(C_2H_5) < \mu(CH_3) < \mu(CH_2OH) < \mu(N(CH_3)_2)$$
$$< \mu(NH_3^+Cl^-) < \mu(NH(CH_3)_2^+Cl^-) \lesssim \mu(NH_2CH_3^+Cl^-) < \mu(NHCH_3)$$

As in the case of allene derivatives[2], a nomenclature based on the sequence of values of the parameter μ can be proposed for methane derivatives. If we designate as the (R_μ) or (S_μ) configuration of a methane derivative an arrangement of ligands that correspond to the definition of *R* and *S*, but unlike the latter is based on the μ-sequence, then at least for the available data on derivatives having ligands from Table 6 we can say:

Derivatives having the (R_μ) configuration are levorotatory, whereas derivatives having the (S_μ) configuration are dextrorotatory.

This should also be true for compounds that are not listed here, provided that only ligands from Table 6 are present and the magnitudes of the experimentally found optical rotations are not extremely small.

4. Summary

The discussion of the available data in relation to the pure structural statements of the theory, *i. e.* without calculation of the optical activity by means of detailed quantum-mechanical formulas and with deliberate limitation of the discussion to the semiempirical aspect of the chirality functions, confirms the second approximation method. On chemical grounds the practical test rules out the use of derivatives having an ideal T_d-situation. The experimental material requires an analysis of the T_d-component and simultaneously of how well it is approximated by expression (2b). Therefore the quantitative reliability of function values should be improved by a further increase in the amount of experimental data.

Even with the existing material, however, the distribution of the values found for $\bar{\Phi}$ in the range $0 \leq |\bar{\Phi}| \leq \bar{M}$ shows beyond any doubt that the separation of the optical rotation into a contribution from a T_d-component formulated by (2b) and others corresponds to well defined

Table 5.

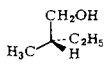
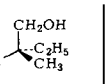
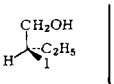
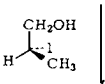
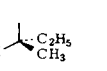
Mixture	Ligand 1					
(1)	$NH_3^+Cl^-$	−5.75 −4.1288 −4.2356	−7.6 −6.2428 −2.7419	−17.2 −15.8428 −18.1659	+19.5 +20.8572 +19.0913	+4.0 +5.3572 +6.0521
(2)	$NH_2CH_3^+Cl^-$	−5.75 −4.1288 −4.2356	−9.3 −7.8178 −3.1801	−20.5 −19.0178 −20.9594	+21.6 +23.0822 +22.0657	+6.4 +7.8822 +6.3093
(3)	$N(CH_3)_2$	−5.75 −4.1288 −4.2356	−2.6 −0.8678 −0.9979	− 9.8 − 8.0678 − 6.7855	+ 3.9 + 5.3622 + 7.0683	+5.7 +7.4322 +4.9506
(4)	$NH(CH_3)_2^+Cl^-$	−5.75 −4.1288 −4.2356	−4.8 −2.9928 −3.1349	−24.2 −22.3928 −20.6723	+18.1 +19.9072 +21.7597	+7.8 +9.6072 +6.2831
(5)	$NHCH_3$	−5.75 −4.1288 −4.2356	−2.88 −1.1528 −5.3197	−36.2 −34.4728 −34.3422	+35.6 +37.3272 +36.4059	+0.7 +2.4272 +7.4916

Table 6.

Ligand	μ-value for mixture				optimum μ-value for mixtures *(1)—(5)*
	(1)	*(2)*	*(3)*	*(4)*	
H	0.0000	0.0000	0.0000	0.0000	0.0000
CH_3	0.8777	1.1296	1.5972	1.4182	1.1287
C_2H_5	0.5175	0.5601	0.9967	0.9595	0.8393
CH_2OH	3.4201	2.8650	2.6164	2.7553	3.1896
$NH_3^+Cl^-$	3.6844				3.4997
$NH_2CH_3^+Cl^-$		3.3981			3.5384
$N(CH_3)_2$			2.9483		3.3205
$NH(CH_3)_2^+Cl^-$				3.3460	3.5345
$NHCH_3$					3.7040

geometrical properties of the methane derivatives. A more detailed analysis has to be based upon this fact.

The polynomial (2a) appears to describe the T_d-contribution in an acceptable approximation, at least for those derivatives having ligands from Table 6, and to predict the correct sign for derivatives whose optical rotations are not too small. It should be profitable on the one hand to continue the test in the form described and on the other to use the results of a quantum-mechanical theory of the phenomenon, which have been completely disregarded here, to correlate the T_d-component and contributions due to deviations from the T_d-situation with physical or geometrical details. It should ultimately be possible to obtain information from the optical activity about preferred conformations in methane derivatives or about changes in the geometric arrangement as a result of association, solvent effects, *etc.* We regard the test carried out here as a first successful step on the way to this goal.

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The Perturbation Treatment of Chemical Reactivity[**]

By Robert F. Hudson[*]

The perturbation method of treating chemical reactions is discussed in a simple manner, by invoking the general hypothesis that the *initial perturbation determines the course of a reaction*. This approach is used to develop a general theory, as an alternative to the transition state theory. Such apparently diverse concepts as the symmetry rules for cyclic processes, and hard and soft acids and bases can be derived by this treatment, which is applied to radical reactions and aliphatic and aromatic substitution.

1. Introduction

The quantitative treatment of reactivity remains one of the most difficult and yet intriguing problems of chemistry, of particular importance in the field of reaction mechanisms. Chemical reactivity is usually discussed in terms of the transition state theory[1], but this method has severe limitations[2] in that neither the activation energy nor the activation entropy can be calculated to within reasonable limits of accuracy, except for the simplest of reactions (*e.g.* $H+H_2$).

The chemist requires an approach which can be applied to large molecules, and he is particularly concerned with the influence of regular structural changes on reactivity and product composition. In recent years the principle of conservation of orbital symmetry, which delineates in a simple way those reactions which can occur and those which cannot, has been particularly successful in dealing with concerted reactions[3]. It is becoming apparent that these rules are part of a wider scheme of treating chemical reactions[4], and of estimating potential energy surfaces in an approximate way. The perturbation theory is central to

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most of these developing methods, and in this article an attempt is made to develop this method in a simple manner which should be intelligible to any experimental chemist. The basic equations will then be applied to a wide range of chemical processes.

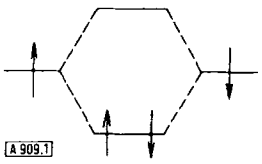


Fig. 1. Interaction of two singly occupied degenerate orbitals.

2. The Perturbation Method

In contrast to the transition state theory, the perturbation method[5] does not normally attempt to calculate the activation energy of a reaction. Rather, the energy change in the initial stages of the reaction as the orbitals of the reactants mutually interact (*i.e.* perturb each other) is calculated, and in effect the initial slope of the potential energy curve is estimated.

The basic idea of the perturbation method is that on the approach of two interacting systems, the combined wave function of the perturbed system is given by appropriate combinations of the wave functions of the two unperturbed molecules. By considering the interaction of each pair of orbitals separately, the total perturbation energy can be found.

The orbitals may interact in various ways depending on their symmetry and relative energies. In the perturbation method, this is represented by a Hamiltonian operator H' which is a modification of that of the initial system H^0, thus

$$H = H^\circ + H'$$

The Schrödinger equation may be solved by the usual variational treatment leading to a set of simultaneous equations

$$\begin{vmatrix} \alpha_1 - E & \beta \\ \beta & \alpha_2 - E \end{vmatrix} = 0 \qquad (1)$$

for the energy E due to the interaction of orbitals ψ_1 and ψ_2 of energy α_1 and α_2 respectively; β is the resonance integral for the specific interaction:

$$\beta = \langle \Psi_1 | H | \Psi_2 \rangle \qquad (2)$$

Two general situations are of importance corresponding to the interaction of degenerate and non-degenerate orbitals.

2.1. Degenerate Orbitals

When $\alpha_1 = \alpha_2$, *e.g.* for the interaction of two identical atoms or radicals, solution of the Schrödinger equation (with neglect of overlap) gives

$$E_+ = \alpha + \beta; \quad E_- = \alpha - \beta \qquad (3)$$

The combination of two orbitals thus gives rise to splitting to give bonding and anti-bonding orbitals (Fig. 1). For two electrons the bond energy is 2β.

For the combination of two organic radicals R and S at atoms r and s respectively:

$$\beta = \langle \Psi_j | H | \Psi_k \rangle = \langle C_{rj}\varphi_j | H | C_{sk}\varphi_k \rangle = C_{rj}C_{sk} \langle \varphi_j | H | \varphi_k \rangle = C_{rj}C_{sk}\beta_{rs}$$

where C_{rj} and C_{sk} are the coefficients for the electron in orbital j at atom r, and in orbital k at atom s respectively. Hence

$$\Delta E = 2C_{rj}C_{sk}\beta_{rs} \qquad (4)$$

This is known as a *first order perturbation.*

As an example[6], consider the dissociation of allylic and benzylic compounds, for which the non-bonding orbital coefficients are given by the Longuet-Higgins rule[7]. The dissociation energy, ΔE, is given by the combination of the appropriate radical and atom X. This is produced mainly by the perturbation[8] of the non-bonding orbital of the radical by the atomic orbital of X.

$$CH_2{=}CH{-}CH_2{-}X \xrightarrow[-1/\sqrt{2}]{1/\sqrt{2}} CH_2{=}CH{-}\dot{C}H_2 + X^\cdot$$

The dissociation energy is given by σ bond and π bond energy changes, *i.e.*

$$\Delta E_A = E_{C-X} + \Delta E_\pi = E_{C-X} + 2\beta(1 - (1/\sqrt{2}))$$

Likewise for the dissociation

$$C_6H_5{-}CH_2{-}X \xrightarrow{(2/\sqrt{7}))} C_6H_5{-}\dot{C}H_2 + X^\cdot$$

we have:

$$\Delta E_B = E_{C-X} + \Delta E_\pi = E_{C-X} + 2\beta(1 - (2/\sqrt{7}))$$

Hence

$$\Delta E_B - \Delta E_A = -2\beta((2/\sqrt{7}) - (1/\sqrt{2})) \approx -0.10\,\beta$$

If $\beta \approx 1$ eV, $\Delta E_B - \Delta E_A \approx 3$ kcal/mol, a value which is close to the difference in bond energies of benzyl and allyl compounds.

By taking the coefficients C_{rj} calculated by a simple Hückel method, *Fukui*[9] has applied this equation to the dissociation energies of various kinds of aliphatic molecules (Fig. 2).

First order perturbations are additive, so for interaction at several points in the molecule,

$$\Delta E = 2\sum C_{rj}C_{sk}\beta_{rs} \qquad (5)$$

This equation is of importance when concerted reactions are considered.

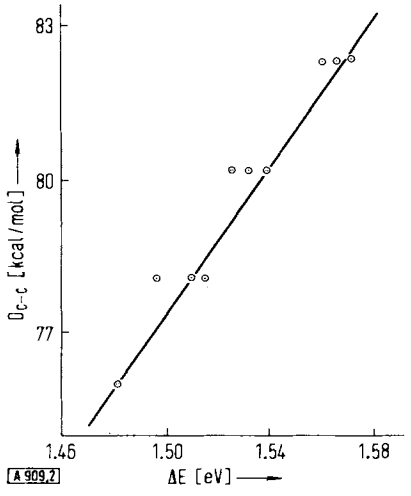


Fig. 2. Comparison of calculated perturbation energies ΔE [eq. (4)] and experimental bond energies D_{C-C} for the hydrocarbons: *n*-hexane (1-methylpentane), 2-methylpentane, 2,3-dimethylbutane, and 2,2'-dimethylbutane.

If the orbitals are doubly filled, then according to equation (3),

$$\Delta E = 2\beta - 2\beta = 0$$

This cannot be exact since the interaction of two closed shells, *e.g.* two helium atoms, leads to a net increase in energy, *i.e.* a repulsion. This can be introduced indirectly by retaining the overlap integral S in the solution of equation (1) which gives

$$E_+ = \frac{\alpha + \beta}{1 + S} \quad \text{and} \quad \frac{\alpha - \beta}{1 - S} = E_- \tag{6}$$

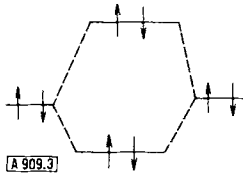


Fig. 3. Interaction of two doubly occupied degenerate orbitals.

For two electrons in each orbital, the change in energy ΔE, on interaction of the two doubly filled atomic orbitals is given by

$$\Delta E = \frac{4\alpha S^2 - 4\beta S}{1 - S^2} \tag{7}$$

If the Mulliken approximation[10] is made, *i.e.* $\beta = KS$, eq. (7) becomes

$$\Delta E = -(K - \alpha)S^2 \tag{8}$$

This relates the repulsion energy of closed shells to the overlap integral, which is amenable to calculation[11].

2.2. Non-Degenerate Orbitals

Usually $\alpha_1 \neq \alpha_2$, *i.e.* the interacting orbitals are non-degenerate. This corresponds to the interaction of an electron donor (a 2-electron orbital) of energy α_1, with an unoccupied level of an electron acceptor, α_2.

Solution of eq. (1) then gives

$$E = \frac{\alpha_1 + \alpha_2}{2} \pm \sqrt{(\alpha_1 - \alpha_2)^2 + 4\beta^2} \tag{9}$$

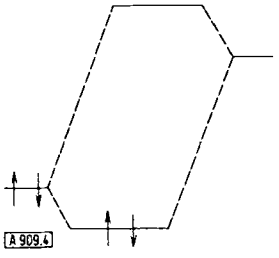


Fig. 4. Interactions of a doubly occupied orbital of energy α_1 with an unoccupied orbital of energy α_2.

If $\alpha_1 \gg \alpha_2$,

$$E = 2\alpha_1 + 2\beta^2/\alpha_1 - \alpha_2$$

Thus

$$\Delta E = 2\beta^2/(\alpha_1 - \alpha_2)$$

By analogy with eq. (4) it follows for interaction between atoms r and s of two molecules R and S that

$$\Delta E = \frac{2(C_{rj}C_{sk}\beta_{rs})^2}{\alpha_j - \alpha_k} \tag{10}$$

This method can be illustrated by calculation of π bond energy changes for the combination of two double bonds to give butadiene. The first order perturbation energy is *ca.* zero (S neglected), but the second order term gives an energy of 0.5 β (cf. resonance energy of 0.48 β by the Hückel method).

In general the situation is more complex, and the interaction of several filled orbitals, j, of the donor *e.g.* a conjugated nucleophile or aromatic hydrocarbon, with acceptor orbitals k must be considered. These perturbations are additive and the total energy then becomes[5]

$$\Delta E = 2\sum_{j}^{occ}\sum_{k}^{unocc}\frac{C_{rj}^2 C_{sk}^2 \beta_{rs}^2}{\alpha_j - \alpha_k} \tag{11}$$

In some reactions, several atoms of each molecule interact mutually in the transition state, and hence the appropriate wave functions, Ψ_j and Ψ_k must be used [cf. eq. (5)]. In the general case where filled orbitals j of molecule R interact with vacant orbitals k of molecule S, and filled orbitals k of molecule S interact with vacant orbitals j of molecule R, we have[5]:

$$\Delta E = 2\sum_{j}^{occ}\sum_{k}^{unocc}\frac{(\Sigma C_{rj}C_{sk}\beta_{rs})^2}{\alpha_j - \alpha_k} + 2\sum_{k}^{occ}\sum_{j}^{unocc}\frac{(\Sigma C_{rj}C_{sk}\beta_{rs})^2}{\alpha_k - \alpha_j} \tag{12}$$

This equation applies particularly to cycloadditions and similar concerted processes (see Section 8). In the special case where a particular orbital k localized on atom s of molecule S interacts with orbitals j of R (*e.g.* as in some simple π-complexes), eq. (12) simplifies to

$$\Delta E = 2\sum_{j}^{occ} \frac{(\Sigma C_{rj}C_{sk}\beta_{rs})^2}{\alpha_j - \alpha_k} \qquad (13)$$

When polar molecules are involved, allowance must be made for the Coulombic attraction and interelectronic repulsion. A polyelectronic perturbation treatment[12] which introduces nuclear-nuclear and electron-electron interaction explicitly, within the framework of a central field approximation, into the Hamiltonian operator leads to the following approximate equation for the perturbation energy,

$$\Delta E \simeq q_r q_s \Gamma_{rs}\, 1.2 + 2\sum_{j}^{occ}\sum_{k}^{unocc} \frac{C_{rj}^2 C_{sk}^2 \beta_{rs}^2}{\alpha_j - \alpha_k} \qquad (14)$$

where q_1 and q_2 are the formal charges on r and s.

The one electron Hamiltonian operator, H is replaced by $H = H' - (e^2/R_{rs})$ and the electron-electron interaction is given by

$$\int \varphi_i(1)\,\varphi_k(2)\,H\varphi_j(1)\,\varphi_i(2)d\tau_1 d\tau_2$$

The core-core interaction is given by the energy $Z_R Z_S e^2/R_{rs}$.

Eq. (14), which reduces to eq. (11) for the interaction of neutral species, is of particular use in the interpretation of nucleophilic substitutions (see Section 3).

3. Reaction Paths

The energies calculated by the procedures given in Section 2 refer to small interactions only, as under these conditions the wave function of the combined system can be adequately represented by a combination of the ground state functions. A chemical reaction proceeding through a transition state, however, involves considerable displacement of the nuclei, and we must therefore ask the question, "under what conditions does the initial perturbation represent the chemical reactivity"?

Let us consider, for example, the interaction of an electron donor with a C—Cl bond, the orbitals of which are given by

$$\psi_+ = C_1\varphi_C + C_2\varphi_{Cl} \quad \text{and} \quad \psi_- = C_2\varphi_C - C_1\varphi_{Cl}$$

where $C_2 > C_1$. This means that the electron density around the chlorine atom is greater than around carbon, as required by the polarization C→Cl. The mechanism of substitution is explained classically by the attraction of the nucleophile to the carbon atom by Coulombic forces.

Moreover, the coefficient on carbon of the antibonding orbital, ψ_- is greater than that of chlorine ($C_2 > C_1$). Consequently the second term of eq. (14) also directs the nucleophile to the carbon atom, along the line of the C—Cl nuclei, as shown by a consideration of the symmetry of the antibonding orbital (Fig. 5).

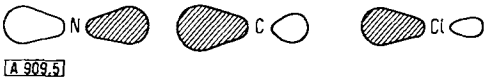


Fig. 5. Interaction of a nucleophile with the antibonding orbital ψ_- of a C—Cl bond in the initial stage of the substitution reaction.

Since the interaction energy is given by eq. (10) *i.e.*

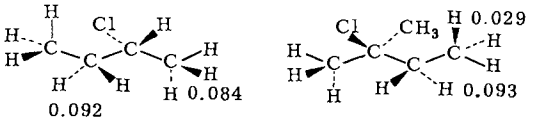
$$\Delta E \sim C_C^2/(\alpha_N - \alpha_E)$$

(where N refers to nucleophile, E to electrophile) the relative reactivities of a series of alkyl halides may be related[13] to C_c, since changes in $1/(\alpha_N - \alpha_E)$ are relatively small (Table 1)[*].

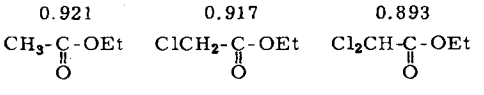
Table 1. Reactivity coefficients for a series of alkyl halides; calculated by the EH method [13].

RCl	α_E [eV]	C_C^2	$C_{\beta-H}^2$
CH_3Cl	1.870	1.091	—
C_2H_5Cl	1.624	0.929	0.0793
$(CH_3)_2CHCl$	1.487	0.914	0.0862
$(CH_3)_3CCl$	1.237	0.847	0.0911

The relative rate of β-elimination is similarly given by the coefficients on the β-hydrogen atom of the lowest unoccupied molecular orbital (LUMO) of the alkyl halide[13] (Table 1). Moreover the Saytzeff rule[14] for the direction of elimination in an alkyl halide is explained by the magnitude of these orbital coefficients as shown by the following examples—the *gauche* form (as required for an *anti*-elimination[**]) being assumed.



In the case of highly polar molecules, however, the reactivity does not usually follow the magnitude of these orbital coefficients[13] *e.g.* the rates of hydrolysis of the following esters change in the reverse order of the coefficients C_c:



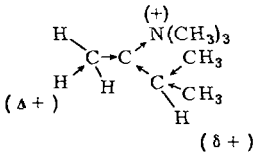
CH_3-C(=O)-OEt $\quad$ $ClCH_2$-C(=O)-OEt $\quad$ Cl_2CH-C(=O)-OEt

The changes are however small, and in this case the increasing charge on the carbonyl carbon atom determines the reactivity order, *i.e.* the first term of eq. (14) is dominant.

[*] Because of the low energy of the nucleophile orbital compared with α_E.

[**] Calculations show that the value of $C_{\beta-H}$ is a maximum for this configuration, thus predicting *anti*-elimination [15].

Similarly the Hoffmann rule for elimination in onium salts leads to a reverse order of rate of elimination to that given by the Saytzeff rule[14]. Here Coulombic forces may control the reaction[*], as given by the large inductive effects first considered by *Ingold*[16]:



Now, in the case of substitution of an alkyl halide considered above, the interaction given by eq. (10) leads to a combined system (Fig. 4) involving some charge transfer from ψ_N to ψ_-. Accordingly, the anti-bonding orbital ψ_- becomes partially occupied, *i.e.* the C—Cl bond becomes more antibonding, with a consequent weakening and slight displacement of the nuclei along the reaction coordinate. This parallelism between charge transfer and bond exchange has recently been discussed by *Fukui*[17] on the basis of the simple Hückel treatment

For the i-th MO

$$(\alpha_r - E_i)(C_r^i)^2 + \Sigma C_r^i C_s^i \beta_{rs} = 0$$

where the summation extends over neighbouring atoms, *i.e.*

$$\sum_s (C_r^i)(C_s^i) = \frac{\alpha_r - E_i}{(-\beta_{rs})} (C_r^i)^2 \qquad (15)$$

The energies of occupied orbitals are usually lower than α_r, and those of unoccupied orbitals are higher. Thus the summation term is positive for occupied MOs and negative for unoccupied MOs. Hence the position of largest coefficient density in the HOMO and in the LUMO[**] is liable to weaken bonds with neighboring atoms in the charge transfer process.

Further extension of the C—Cl bonds, as required to reach the transition state, leads to regular changes in orbital energies and coefficients. As the overlap decreases,

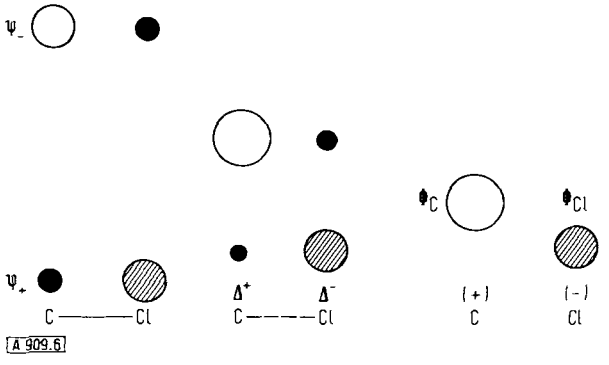


Fig. 6. Loosening of a C—Cl bond with charge transfer in nucleophilic substitution.

[*] The Brønsted β value is much greater for the elimination of onium salts than for neutral substrates [16b].

[**] HOMO = highest occupied molecular orbital; LUMO = lowest unoccupied molecular orbital.

the energy of ψ_- decreases which reduces the gap between α_N and α_E until the nuclei are separated (Fig. 6). At the same time, C_{Cl} of ψ_+ and C_C of ψ_- increase to the final value of unity for the separated atoms.

This behavior, similarly to that previously described in an empirical treatment of nucleophilic reactivity[18], is formulated by *Fukui* in the following rules:

1. The position of the largest density in the HOMO or LUMO is also that position most likely to weaken the bonds with neighboring atoms for electron releasing or electron attracting interaction respectively.

2. The energy difference between the orbitals of donor and acceptor decreases as reaction proceeds.

3. The coefficients in these orbitals increase (to the ultimate value of unity) as the reaction proceeds.

These changes are more pronounced for σ bonds than for π-bonds, in view of the greater influence of the overlap integral in saturated systems, and lead to re-hybridization as in the formation of an S_N2 transition state. The reaction progress involves the conversion of the initial orbitals into 3 molecular orbitals characterizing the transition state as shown by the correlation diagram in Figure 7.

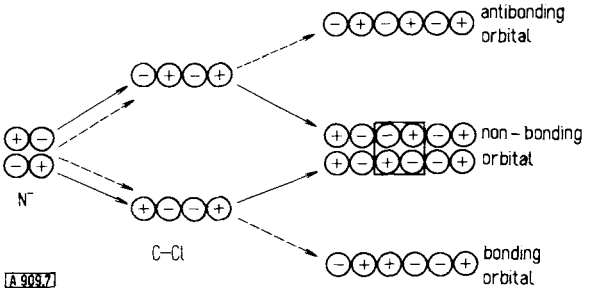


Fig. 7. Correlation diagram for the interaction of an electron donor with a C—Cl bond.

It is seen that the interaction of the nucleophile orbital with the antibonding orbital of the electrophile transforms into the non-bonding orbital (expressed originally[19] as a resonance hydrid of N^-RX and $NR\ X^-$). The initial perturbation thus directs the formation of the transition state.

It is now necessary to discuss the general experimental method which provides information on the extent of interaction between the reactants leading to the transition state. The interaction of two *similar* nucleophiles of orbital energies α and α′ with an acceptor orbital, ψ*, of energy α_s and coefficient C_s at the reaction site (Fig. 8) leads to a difference in second order perturbation energy $\Delta\Delta E$:

$$\Delta\Delta E = \frac{2C_s^2\beta^2}{\alpha - \alpha_s} - \frac{2C_s^2\beta^2}{\alpha' - \alpha_s} \approx 2C_s^2 \frac{(\alpha' - \alpha)}{(\alpha - \alpha_s)^2}\beta^2$$

Similarly for the interaction with an atomic orbital, φ_s, of energy α_s^0, leading to the formation of a covalent bond,

$$\Delta\Delta H \approx \frac{2\beta^2(\alpha' - \alpha)}{(\alpha - \alpha_s^0)^2}$$

so that

$$\Delta\Delta E \approx C_s^2\left(\frac{\alpha-\alpha_s^0}{\alpha-\alpha_s}\right)^2 \Delta\Delta H$$

i.e.

$$\Delta\Delta E \approx \chi\cdot\Delta\Delta H \qquad (16)$$

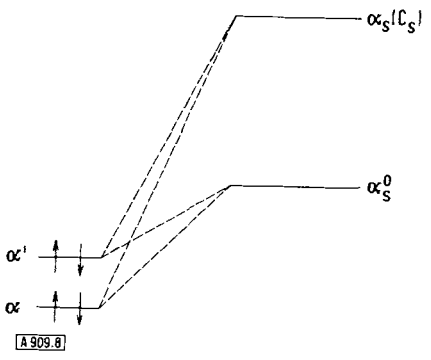


Fig. 8. Interaction of two similar nucleophiles with acceptor orbitals.

Accordingly, when $\alpha_s \ll \alpha_s^0$, $\chi \to 0$, and as $\alpha_s \to \alpha_s^0$ and $C_s \to 1$, $\chi \to 1$.

These are the boundary conditions for a generalized *linear free energy relationship*, usually derived[*] parametrically[20] or from potential energy profiles[21]. Thus for reaction at a hydrogen atom (neglecting differences in entropy), the Brønsted relation is derived,

$$\log k/k' = \chi(pK_a - pK_a') \qquad (17)$$

The value of χ for a particular reaction changes considerably with the nature of the substrate. Thus in the base catalyzed enolization of ketones[22], χ changes from *ca.* 0.9 to 0.4 as the basicity of the displaced anion decreases. Bond formation in the transition state is therefore more advanced with the less basic nucleophile, a rule first deduced by *Swain*[23].

In β-elimination, the magnitude of χ changes[16b, 24] from 0.17 to 0.88 representing a change from the E_1 to the E_1CB type of transition state[25].

Eq. (17) is now applied to reactions at a wide range of electrophilic centers[26] and although anomalies are found[26], χ usually provides a measure of the interaction in the transition state. In aromatic chemistry, the rate of electrophilic substitution of a range of polycyclic alternant hydrocarbons is related logarithmically to the basicity[27] as represented by the protonation equilibria in HF. Similarly, the relative reactivity of two similar aromatic compounds, *e.g.* toluene and benzene, towards different electrophiles gives a measure of the extent of interaction in the transition state as assumed in the rule of *Brown* and *Nelson*[28]. Since the selectivities[**] given in this way vary from *ca.* 1.5 to 10^4, a wide range of transition state structures, as found for S_N2 and E_2 reactions must occur. The transition state may thus differ considerably in structure from a Wheland intermediate[29].

We reach the general conclusion therefore that the magnitude of the coefficient of a linear free energy relationship (LFER) (sometimes referred to as reagent selectivity) is a measure of the perturbation between the reactants in the transition state.

The generalized LFER is a quantitative statement of the non-crossing rule[30] (not to be confused with the identically named rule in correlation diagrams). Moreover, the perturbation energy is a measure of $\partial E/\partial r$, *i.e.* the initial slope of the potential energy curve. As seen from the schematic representation in Figure 9 activation energy differences are given by differences in these slopes $(s_1 - s_2)$, provided that the energy profiles for two similar reactions have similar shapes[*]. Thus, when the non-crossing rule holds,

$$\Delta\Delta E \sim \Delta s \sim \Delta\Delta H \qquad (18)$$

a relationship which can be derived analytically[31].

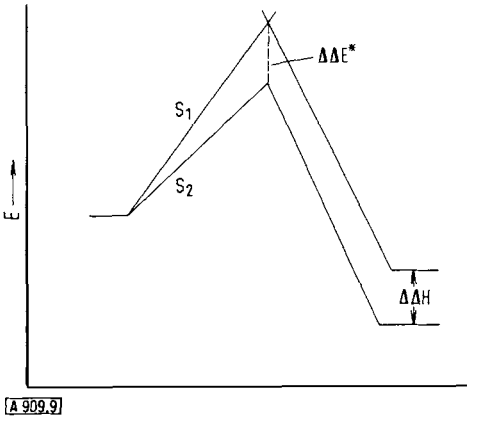


Fig. 9. Schematic representation of the energy profiles of two similar reactions.

It follows therefore that the perturbation energy usually determines the reaction path, and provides a measure of reactivity if the non-crossing rule holds.

4. Radical Abstraction Reactions

Radical reactions may be treated in the same way as nucleophilic substitutions, but here the interaction with occupied orbitals also must be considered. According to Figure 10, perturbations of various kinds have to be considered, but to a first approximation[32] [(cf. eq. (12)],

$$\Delta E = \sum_k^{occ} \frac{C_{rj}^2 C_{sk}^2 \beta_{rs}^2}{\alpha_j - \alpha_k} - \sum_k^{unocc} \frac{C_{rj}^2 C_{sk}^2 \beta_{rs}^2}{\alpha_j - \alpha_k} \qquad (19)$$

[*] χ is used in the place of β to avoid confusion of the Brønsted coefficients (β) with the resonance integral β.

[**] Defined as reactivity relative to that of benzene.

[*] This assumption is made in all derivations of linear free energy relationships.

The perturbation energy, ΔE, (eq. 10) is a stabilization whereas the P.E. of the reacting system increases (Fig. 9). This increase is due to the repulsion term (eq. 7) which for simplicity is taken to be constant. It is readily introduced [75] into eq. 10. According to the present treatment, differences in S are due mainly to changes in ΔE.

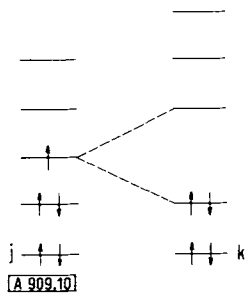


Fig. 10. Interaction of a singly occupied orbital ψ_j with the HOMO- and LUMO orbitals ψ_k.

In general, the interaction of the singly occupied j level with the highest occupied and lowest unoccupied k orbitals will determine the perturbation energy.

Let us consider the interaction of a radical R˙ with a saturated hydrocarbon R'CH_2—H (Fig. 11). The C—H bond is originally formed by the combination of C and H atomic orbitals as shown in Figure 11. Owing to the overlap term [eq. (6)], the energy of σ^* is usually very high (see Table 1) and consequently R˙ interacts more strongly with σ than with σ^*. In other words, radicals behave as weak electrophiles[*], as shown for example by the ρ values[33] in reactions of substituted toluenes ($\rho = -1.46$ for $CCl_3^{\cdot}$; -1.36 for $Br^{\cdot}$ and -1.08 for $(CH_3)_2N^{\cdot}$).

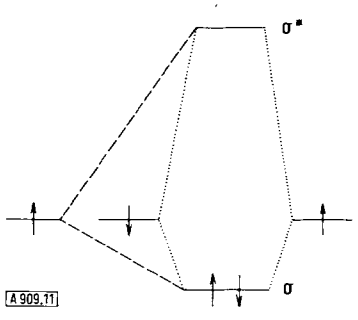
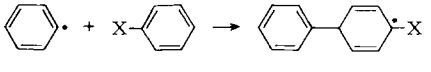


Fig. 11. Interaction of a radical with the C—H bond of a saturated hydrocarbon.

The reactivity of a series of radicals with various alkanes, as given by eq. (19), is shown in Figure 12, and the agreement is seen to be very satisfactory.

A wide range of radical abstraction reactions can be treated in this way including the extraction of halogen atoms from alkyl halides by alkyl radicals, sodium atoms and hydrogen atoms. The calculated perturbation energies are compared with experimental activation energies (ΔE^*) for two series of alkyl halides in Table 2.

[*] This is not necessarily the case for other types of radical reaction. Addition to aromatic systems is assisted by both electron donating and electron attracting substituents, *e.g.*



This is because π^* orbitals are usually lower in energy than σ^* orbitals, and hence the interactions of the lone electron with π and π^* levels are comparable.

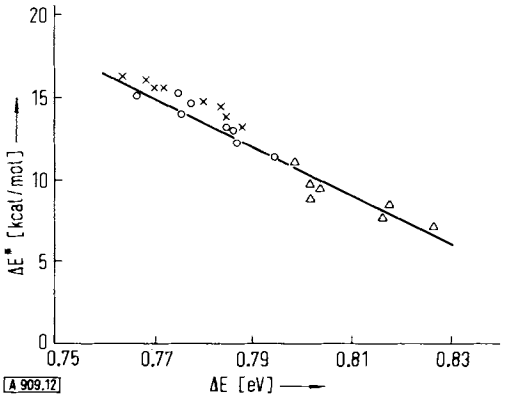


Fig. 12. Comparison of the activation energy, ΔE^*, for the radical abstraction from saturated hydrocarbons and the perturbation energy, ΔE, [eq. (19)].

Table. 2. Comparison of perturbation energy and activation energy for some radical abstraction reactions [32].

$RCl + Na \rightarrow R^{\cdot} + NaCl$		
	ΔE [eV]	ΔE^* [kcal/mol]
CH_3Cl	1.379	9.7
C_2H_5Cl	1.404	9.5
i-C_3H_7Cl	1.494	8.9
tert-C_4H_9Cl	1.496	8.0

$CH_nCl_{4-n} + H \rightarrow CH_nCl_{3-n}^{\cdot} + HCl$		
	ΔE [eV]	ΔE^* [kcal/mol]
CH_3Cl	1.379	7—9
CH_2Cl_2	1.756	6
$CHCl_3$	3.20	4.3
CCl_4	3.83	3.5

The relative rate of hydrogen abstraction from various positions in complex alkanes can be predicted[32] and average values of the relative reactivity of primary, secondary and tertiary H atoms are given in Table 3.

Table 3. Values of perturbation energies, ΔE, and reaction rates for hydrogen atom abstraction from alkanes.

H atom	ΔE [eV]	$10^{-3}k$[l/mol s] at 180 °C
CH_4	0.993	—
prim. C—H	1.004	0.3
sec. C—H	1.014	2.7
tert. C—H	1.033	15

5. Stabilized Radicals

Radicals can be stabilized in two main ways:

1. By conjugation as in the benzyl and allyl radicals (see Section 2.1). Here the energy of the lone electron in a non-bonding orbital is similar to that of a methyl radical[*]. Since the perturbation energy [eq. (19)] depends on the orbital coefficient, C_{rj}, of the terminal atom of the radical, the methyl radical ($C_{rj} = 1$) is more reactive than the benzyl radical ($C_{rj} = 2/\sqrt{7}$). The same conclusion is reached

[*] This shows the limitation of the simple HMO tretment. Electron repulsion differences lead to a lower ionization potential for the benzyl radical [34].

by calculating the resonance energy of the benzyl radical and then relating reactivity to thermodynamic stability. Thus a benzyl radical is formed more readily than a methyl radical (p. 37) and conversely it is less reactive. This is not always the case however. For example $\cdot CH_2—CN$ is a stable radical but it is formed less readily from $CH_3—CN$ than $C_2H_5^{\cdot}$ is from C_2H_6. This must be due to increased C—H bond energy in the ground state of CH_3CN. Hence the perturbation energy is less as required by [eq. (19)].

2. Certain radicals are stabilized by 3-electron bonds[35]. In MO terms, an orbital containing 2 electrons interacts with a singly occupied orbital according to eq. 6 to give orbital splitting, *e.g.* for the degenerate case

$$\Delta E = \frac{2\alpha + 2\beta}{1+S} + \frac{\alpha - \beta}{1-S} - 3\alpha = \frac{(\beta - \alpha S)(1-3S)}{1-S^2}$$

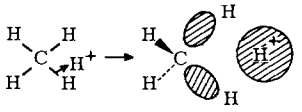
Since, in practice, $\beta > \alpha S$ the radicals are stabilized if $S_{12} < 0.33$. A consideration of overlap integrals[11] suggests that for $p_\pi - p_\pi$ interaction, S_{12} is usually less than 0.25. Consequently radicals such as $R_2N—O^{\cdot}$ (cf. NO), $RO_2^{\cdot}$, $R\dot{C}HOR$, $R\dot{C}HCl$ are stabilzed in this way, and their reactivity is less than that of a simple radical[*].

Thus in contrast to the greater reactivity of HO_2^- compared to that of HO^-, $HO_2^{\cdot}$ radicals are less reactive[37] than $RO^{\cdot}$ radicals in the abstraction of hydrogen from toluene (*e.g.* $\Delta \log k \approx 4.0$ for $HO_2^{\cdot}$ and $(CH_3)_3CO^{\cdot}$ radicals) and in the oxidation of certain organometallic reagents[38].

The stability of radicals of this kind explains the recently proposed radical pair mechanisms[39] for the Stevens, Meisenheimer, Wittig[40] and related rearrangements. It is possible that some aromatic rearrangements *e.g.* benzidine[41] and Fischer-Hepp may proceed through intimate radical pairs.

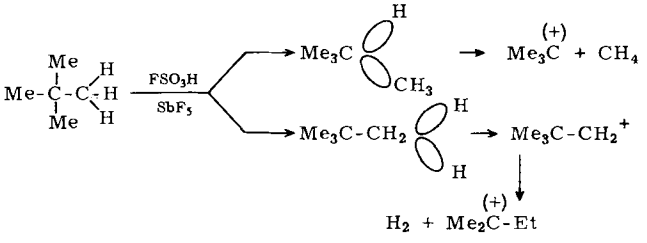
6. Electrophilic Aliphatic Substitution

To take the treatment one stage further, σ-bonds should interact strongly with electrophilic centers, but until recently few such reactions have been investigated. The basic reason is that most electrophiles, *e.g.* H^+, NO_2^+, Cl^+, CH_3CO^+, R^+, are very strongly solvated or complexed in solution, which effectively increases the energies of the corresponding "unoccupied" orbitals. Certain organometallic compounds are reactive electrophiles and mercuration[42] in particular has been studied mechanistically. In contrast to S_N2 processes, most reactions proceed with retention of configuration[42][**]. The transition state thus resembles "electron-deficient" compounds *e.g.* the boron hydrides and certain metal alkyls, in having 3 center 2-electron bonds[43]. The detection of stable CH_5^+ ions in the gas phase[44] shows that in the absence of solvent, the interaction between σ-bonding electrons and a 1s hydrogen orbital is strong. By analogy with radical reactions (Fig. 11) the energies of the σ-orbital and 1s H orbital are probably similar and lead to a strong perturbation:

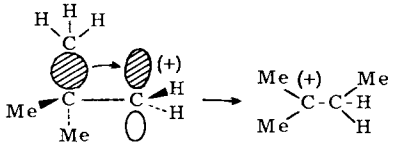


The carbon atom preserves its tetrahedral symmetry, rather than adopting a bipyramidal configuration[45].

Electrophilic protolysis and alkylation proceed by similar interactions[46] *e.g.*



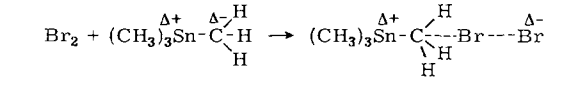
The final Wagner-Meerwein rearrangement proceeds by an intramolecular perturbation of the same kind, *viz.*



This type of interaction in the ground state, which is a second order perturbation, is equivalent to hyperconjugation[*] involving small overlap of the mixing orbitals.

[*] It is to be noted that electrostatic factors influencing the state of hybridization may oppose and reduce the importance of this orbital splitting. Thus, whereas the $CH_3^{\cdot}$ radical is planar, the radical $\cdot CH_2F$ like $NH_2O^{\cdot}$ retains the pyramidal structure [36].

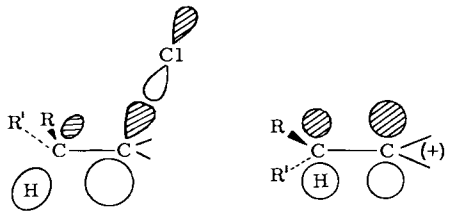
[**] Some organometallic compounds react with inversion of configuration (*F. R. Jensen* and *D. D. Davies*, J. Amer. Chem. Soc. *93*, 4048 (1971); *F. R. Jensen*, *V. Madan*, and *D. H. Buchanan*, *ibid.*, 5283) which may be due to the polarity of the bond. The carbon atom then acts as a carbanion in a typical interaction with an electrophile, *viz.*



[*] The use of this word is perhaps unfortunate in view of the controversy which surrounds this concept. We take it to mean orbital mixing leading to an energy decrease; σ-σ* interactions are particularly weak and must involve other orbitals near the continuum.

This interaction ($\sigma - \sigma^*$) also determines the stereochemistry of all 1,2-rearrangements, *e.g.* Beckmann, Schmidt, Lossen on nitrogen, Baeyer-Villiger oxidation, hydroperoxide rearrangements, and E_2 eliminations. Rearrangements to a carbanionic site (*e.g.* Stevens, Meisenheimer) are symmetry forbidden.

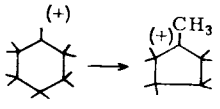
The perturbation approach can explain many apparent anomalies and structural effects, difficult to explain in classical terms; *e.g.* the anomalous gas phase acidity order for alcohols (*J. I. Brauman* and *L. K. Blair*, J. Amer. Chem. Soc. *90*, 6561 (1968)) may be attributed to $n \rightarrow \sigma^*$ and other stabilizing interactions. These are much weaker for amines (large ionization potentials) and the same basicity order is found as for aqueous solution. Weak perturbations involve many acceptor orbitals, *e.g.* the influence of sulfur on stabilizing carbanions and in assisting E_2 reactions (*e.g.* $MeS \cdot CH_2CH_2Cl$) may involve $n \rightarrow \sigma^*$, $p_\pi—d_\pi$, $2p_\pi—4p_\pi$ interactions since the σ^*, d_π, $4p_\pi$ levels may have similar energies (so-called polarization orbitals). The summation of eq. 11 then gives a measure of polarization energy.



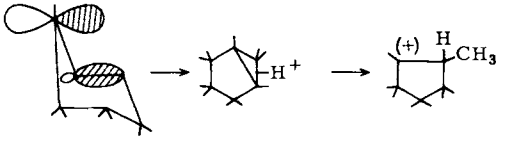
"hyperconjugation" stabilized carbonium ion

The large decrease in ionization potential of the radicals $CH_3^{\cdot} > CH_3CH_2^{\cdot} > (CH_3)_2CH^{\cdot} > (CH_3)_3C^{\cdot}$ is due to the same cause, but this is effectively a strong first order perturbation (approximately).

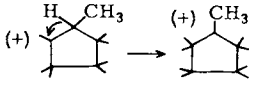
Rearrangements of this kind may proceed by several stages involving second order perturbation, *e.g.*



This involves the mutual perturbation of a C—C σ-bond and a p-orbital of a classical carbonium ion in the first stage, *viz.*



Similar interaction of the tertiary C—H bond[*] and carbonium ion leads to the most stable product[47].



According to *Olah*, non-classical carbonium ions—*e.g.* the norbornyl ion[48] (Fig. 13)—should be regarded as

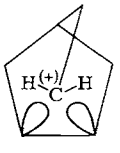


Fig. 13. Norbonyl cation.

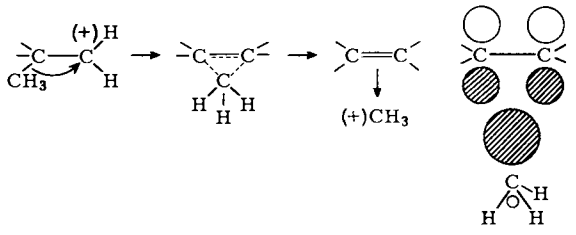
derivatives of CH_5^+, and other electrophilic displacements on carbon—*e.g.* nitration by nitryl salts—proceed through similar intermediates, *e.g.*

$$R{-}H \xrightarrow[CH_2Cl_2/\text{sulfolane}]{NO_2^+PF_6^-} R{-}NO_2 + H^+$$

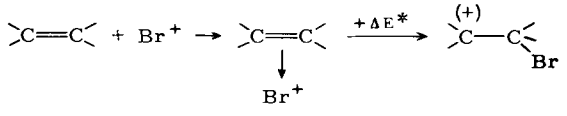
[*] The reactivity of $R_3C{-}C$, $R_2CH{-}C$, $RCH_2{-}C$ follows the ease of homolysis of these bonds.

7. π-Complexes and Aromatic Substitution

The perturbation described above may lead to a symmetrical intermediate usually termed a non-classical carbonium ion[*]. This structure may be regarded as a π complex[50], formed from a π orbital and a vacant sp^3 orbital of a migrating alkyl or aryl group.



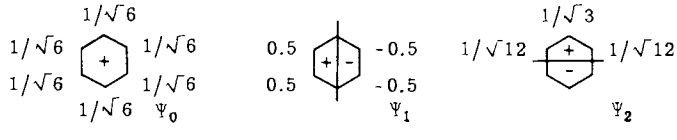
The mechanism of electrophilic addition to olefins has recently been explained in a similar way[51]. Thus most electrophiles, *e.g.* Br^+, I^+, give stable π-complexes, which react further with anions.



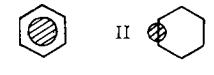
Protons however form a more stable σ-complex, owing to the small overlap with 2 carbon atoms, and the high C—H bond energy.

π-Complexes are of particular interest in the reactions of aromatic compounds although their exact role is still a matter of controversy[52]. The interaction energy can be calculated from eq. (13) since perturbation methods are particularly suitable for calculating weak interactions[53]. In detailed treatments, dispersion and polarization forces must also be taken into consideration.

Let us consider the interaction of benzene with the S and σ* orbitals of acceptors. The occupied orbitals of benzene have the following symmetry:



Two kinds of simple π complex have been detected, the centrosymmetric structure (I)[54], the asymmetric structure (II)[55].



The relative stabilities can be calculated from eq. (13)

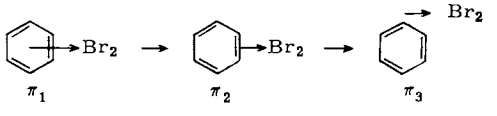
$$E_I = 2(6/\sqrt{6})^2\beta_I^2/(11.5 - \alpha_s)$$
$$E_{II} = 2(2\cdot 0.5)^2\beta_{II}^2/(9.25 - \alpha_s) + 2(2/\sqrt{6})^2\beta_I^2/(11.5 - \alpha_s)$$

[*] The structures and energetics of these intermediates are still the subject of much controversy [49].

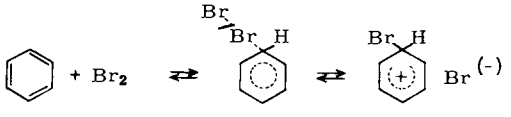
Relative values of β_I and β_{II} can be obtained from the corresponding overlap integrals[56] using the Mulliken approximation[10] (see Section 2.1.). It is readily apparent that structure I is promoted by low values of α_s, *i.e.* low electron affinities (*e.g.* Cl_2, I_2, Br_2, $E_A \approx 0$) and structure II by large values of α_s (*e.g.* Ag^+, I.P. 7.6 eV). Thus we reach the general conclusion that *the symmetry of the π complex formed by a donor with acceptor orbitals of a given symmetry, depends on the magnitude of the perturbation.*

This method has been used by *Herndon et al.*[57] to predict the orientation of π-complexes by an extended Hückel type of procedure. The predicted orientations are not always in agreement with X-ray structures[58], but the energy differences are small in most cases.

We may now apply these considerations to aromatic substitution[29], *e.g.* bromination. If the progress of the reaction is regarded as a gradual extension of the Br—Br bond, the energies of the σ and σ* orbitals (cf. Br_2) tend to approach each other as described previously (Fig. 6). Consequently the perturbation increases as $\alpha_j - \alpha_k$ decreases, and according to the argument presented above, produces a change in structure of the π-complex from π_1 to π_2.



Finally, more energy is required to localize the halogen atom on carbon as in π_3, and hence this structure is at an energy maximum, *i.e.* at the transition state[*]. Further increase in perturbation leads to rehybridization with decrease in energy on formation of the σ complex[59]. Structure π_3 is equivalent to the partially formed σ complex usually taken as the transition state for the rate determining stage of electrophilic substitution[60]:



Accordingly the formation of the transition state involves the perturbation of the π system at a particular carbon atom as originally proposed by *Fukui et al.*[61] and *Brown*[62] to form a "pseudo π-orbital". For this interaction, eq. (11) becomes

$$\Delta E = 2C_{sk}^2\beta_{rs}^2 \sum_j^{occ} \frac{C_{rj}^2}{\alpha_j - \alpha_k}$$

If $\alpha_j - \alpha_k$ is large, *i.e.* if the σ* orbital of the electrophile lies near to the continuum (*e.g.* E_A of $Br_2 \approx 0$) then $1/(\alpha_j - \alpha_k) \approx 1/\alpha_j$ and hence

$$\Delta E = 2C_{sk}^2\beta_{rs}^2 \sum_j^{occ} \frac{C_{rj}^2}{\alpha_j} \qquad (20)$$

[*] Cf. the mechanism of alkyl group migration, *e.g.* the Jacobsen rearrangement.

The term

$$\sum_j^{occ} \frac{C_{rj}^2}{\alpha_j}$$

called *superdelocalizability* by *Fukui*[61] gives a satisfactory measure of the relative reactivity of the various positions in polycyclic hydrocarbons (Fig. 14). Since the highest occupied orbital (HOMO) interacts most strongly with σ*, this is usually the most important orbital in directing the substitution. Accordingly the isomer distribution in the substitution of a particular aromatic hydrocarbon is determined by the magnitude of these coefficients in the so-called "*frontier*" *orbitals*[61].

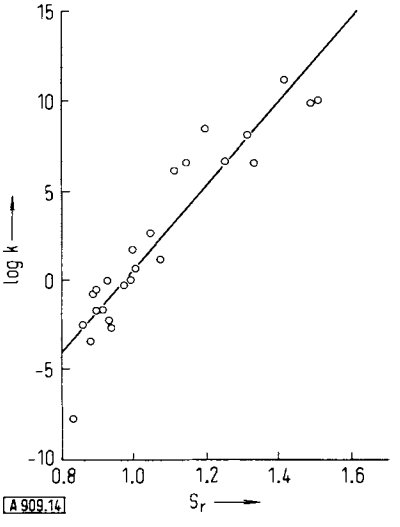
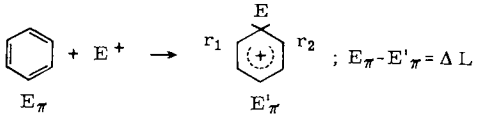


Fig. 14. Relationship between superdelocalizability and rate of nitration of polycyclic aromatic hydrocarbons.

Various reactivity indexes have been developed to represent the rate of aromatic substitution, and it is interesting to note that these have similar degrees of success. The localization energy, ΔL, *i.e.* the energy required to localize the π electrons at the reaction center for formation of the σ-complex is widely used[63].



This may be found by calculating the π-electron energies of ground state and σ-complex, or by the approximate method developed by *Dewar*[64], who pointed out that the Wheland complex is an odd alternant hydrocarbon characterized by a non-bonding orbital, the coefficients of which can be obtained simply by the Longuet-Higgins method[7]. Combination of this non-bonding orbital of the π system of the Wheland complex with a degenerate carbon $2p_\pi$ orbital to give the π system of the original hydrocarbon involves an energy change, ΔE_π, given by

$$\Delta E_\pi = 2(C_{r_1}^0 + C_{r_2}^0)\beta_{C=C} \qquad (21)$$

Since $-\Delta E \sim \log k$ it follows that $\log k \sim (C_{r_1}^0 + C_{r_2}^0)$[*]. Linear relationships of this kind have been observed for a wide range of aromatic substitutions[64]. The slopes of these linear relationships vary considerably with the nature of the reaction leading to values of β (*ca.* 3–13 kcal/mol) *i.e.* considerably less than the value of β for a carbon $p_\pi - p_\pi$ bond. The discrepancy is explained by assuming incomplete bond formation and hence partial bond delocalization in the π system in the transition state[111].

The linearity of the $\log k - \Delta E_\pi$ relationships (Fig. 15) depends on the general linear free energy relationship (cf. eq. (18)) and hence localization energies can only give a measure

$$\Delta\Delta E^* \sim \Delta\Delta H \sim L \qquad (22)$$

of reactivity providing that the non-crossing rule holds. As explained in Section 3 pertubation energy changes are also directly related to $\Delta\Delta E$ providing this rule holds, and this appears to be the basic reason[31] why an index such as superdelocalizability and localization energy are equally satisfactory measures of chemical reactivity particularly of alternant hydrocarbons. (cf. Figs. 14 and 15).

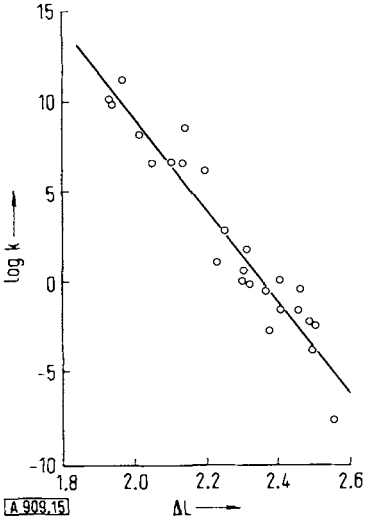


Fig. 15. Relationship between localization energy (L) and rate of nitration of polycyclic aromatic hydrocarbons.

8. Symmetry Controlled Reactions

A great deal has been written in recent years concerning the dominant role played by orbital symmetry in chemical reactions[65]. We shall here simply show how the perturbation method, applied in the same way as in the preceding examples, leads to the Woodward-Hoffmann symmetry rules, which are usually derived from correlation diagrams[66]. In the latter method the symmetries of the orbitals of reactants and products must be known, and also the order of orbital energies.

[*] Changes in σ bond energies and in ΔS^* are assumed to be the same for reactions of similar molecules.

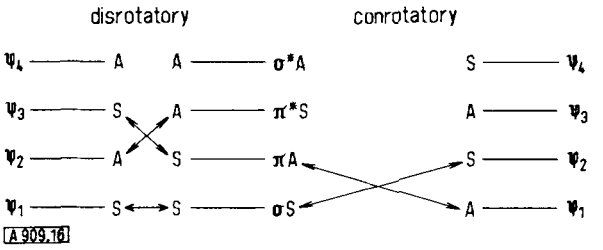


Fig. 16. Correlation diagram for the transformation of cyclobutene into butadiene.

In the perturbation method, the symmetry and coefficients of the orbitals *of reactants only*[*] must be known. As pointed out by *Salem*[4], it is intriguing to note that once again the initial perturbation decides the reaction path.

Let us consider the well known case of the ring opening of cyclobutene, the order of the orbitals is self-evident, *i.e.* σ, π, π*, σ*. In the group theoretical method[66] we enquire into the symmetry of these orbitals as the terminal bonds are rotated in conrotatory or disrotatory modes. These are then correlated with the ψ orbitals of butadiene rotated in the same sense. This gives rise to the correlation diagram in Figure 16.

To illustrate the perturbation method[67], consider the cyclization of butadiene by conrotatory and disrotatory modes.

These rotations produce partial σ bonds, with resonance integral γ. First order perturbation leads to the following interaction energies:

$$\text{conrotatory } \Delta E_c = 2c_{12}\,c_{42}\gamma - 2c_{11}c_{41}\gamma$$
$$\text{disrotatory } \Delta E_d = 2c_{11}\,c_{41}\gamma - 2c_{12}\,c_{42}\gamma$$

Both procedures lead to one incipient bond and one incipient antibond. Now, from the nodal properties of the orbitals, it is apparent that $c_{12} > c_{11}$ and $c_{42} > c_{41}$, hence the conrotatory process leads to greater stabilization[**].

When one electron is promoted from ψ_2 to ψ_3, then interaction of carbon atoms 1 and 4 for orbitals ψ_2 and ψ_3 are equal and opposite, hence

$$\Delta E_d = 2c_{11}\,c_{41}\gamma \quad \text{and} \quad \Delta E_c = -2c_{11}c_{41}\gamma$$

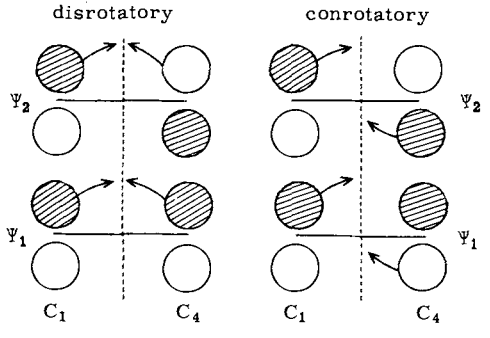


Fig. 17. Disrotatory and conrotatory ring closure of butadiene.

[*] Or the products only.

[**] The energy difference for conrotatory and disrotatory processes is estimated to be 0.89β (*ca.* 30 k·cal/mol). This is of the same order of magnitude as the activation energy differences calculated theoretically [70a].

and the disrotatory mode is favored, as shown by the correlation diagram. The wave functions of polyenes can be represented in closed form[68].

$$C_{rj} = \frac{1}{\sqrt{n+1}} \sin \frac{jr\pi}{n+1} \quad j = 1, 2, 3 \text{ for } \psi_1, \psi_2, \psi_3$$

and hence the above treatment can be generalized[67]. In the case of hexatriene, interaction of the three orbitals at the terminal carbon atoms shows the disrotatory mode to be favored thermally.

$$-\Delta E_c \equiv \Delta E_d = 2c_{13}c_{63}\gamma - 2c_{12}c_{62}\gamma + 2c_{11}c_{61}\gamma$$

Considering now the opening of the cyclobutene ring, the initial perturbation leads to a stabilization when second order perturbation between σ and π^*, and π and σ^* is possible[*]. This is so, as already shown for the analogous ring closure for a conrotatory process (cf. Fig. 18).

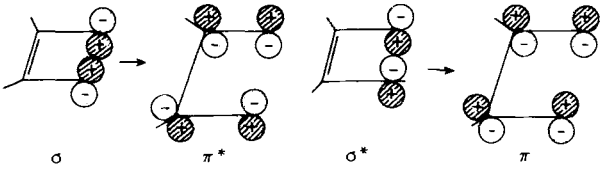


Fig. 18. Orbital interaction of σ with π^* and of π with σ^* in the conrotatory ring opening of cyclobutene.

It is seen therefore that the initial perturbations for ring closing and ring opening processes lead to the same symmetry rules as considerations based on the symmetry of reactants and products. The perturbation approach has the advantage that relative reactivities can, in principle, be calculated from a knowledge of orbital coefficients.

9. Cycloadditions[**]

The calculation of relative reactivities for cyclization reactions, where both stereochemistry and reactivity have been investigated, will now be considered. It is now widely held that $2\pi+2\pi$ and $4\pi+4\pi$ systems cannot cyclize by a synchronous mechanism, whereas $2\pi+4\pi$ reactions, *e.g.* Diels-Alder addition and similar reactions are symmetry allowed[69]. These rules may be extended to σ-systems[70], *e.g.* the hydrogenation of olefins and various addition reactions of diatomic molecules. In particular the addition of hydrogen to halogens is symmetry forbidden. This follows directly from eq. (12) since the initial perturbation involves the interaction of filled bonding and unfilled antibonding orbitals of the two reactants, as shown by the orbital diagram in Figure 19.

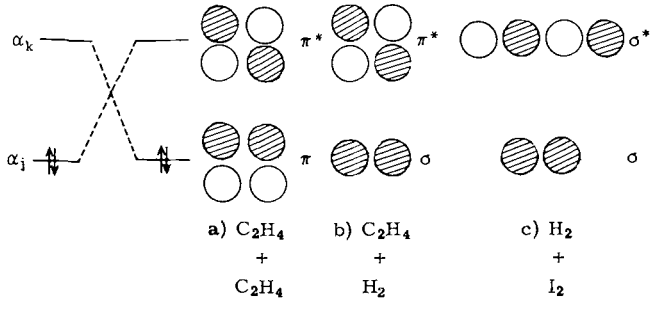


Fig. 19. Orbital interaction between $\pi+\pi$, $\pi+\sigma$, and $\sigma+\sigma$ systems.

The symmetry restrictions can in fact be removed if the reactant (*e.g.* H_2) is initially coordinated to a metal (*e.g.* Pt, Pd) which thus acts as a hydrogenation catalyst. A diimide can similarly add hydrogen in a concerted fashion, as the symmetry is now correct[70] (cf. Fig. 20).

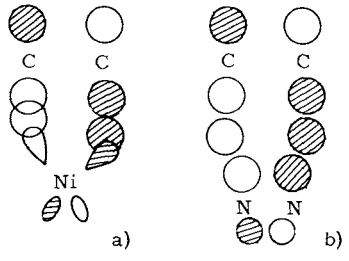


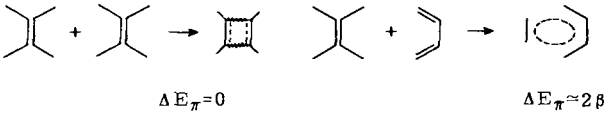
Fig. 20. Catalyzed and concerted hydrogenation of a metal and diimide.

According to eq. (12), the perturbation energy of a system represented by (a)→(c) in Figure 19 is given by

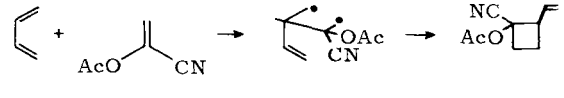
$$\Delta E = \frac{2(C_{rj}C_{sk} - C'_{rj}C'_{sk})^2\gamma^2}{\alpha_j - \alpha_k} + \frac{2(C_{rj}C_{sk} - C'_{rj}C'_{sk})^2\gamma^2}{\alpha_j - \alpha_k} = 0 \qquad (22)$$

since $C_{rj} = C_{sk} = C'_{rj} = C'_{sk}$

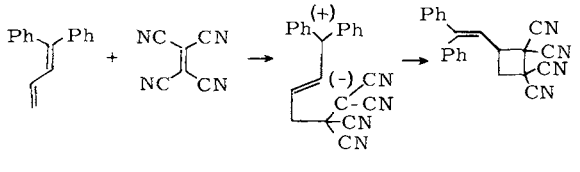
This is equivalent to the explanation originally proposed by *Dewar*[6] that synchonous interaction of two 2π systems leads to the incipient formation of a system resembling cyclobutadiene, *i.e.* $\Delta E_\pi = 0$, whereas $4\pi+2\pi$ systems give a transition state resembling benzene, with positive resonance energy, and hence are energetically favorable.



Thermal reactions of 4π systems should involve radicals[71], *e.g.*



or possibly zwitterions[72], *e.g.*



[*] Sigmatropic rearrangements can be treated in a similar manner.
[**] See also recent articles by W. Herndon, Chem. Rev. *72*, 157 (1972); *N. D. Epiotis*, J. Amer. Chem. Soc. *94*, 1924 (1972).

as inferred from solvent effects. The photochemical cyclization however may be concerted since promotion to π^* leads to positive stabilization (Fig. 21).

Fig. 21. Photochemical cyclization of two 2π systems.

The reactions of dienes with activated olefins (dienophiles) are, on the other hand, symmetry allowed, as shown by the following perturbation treatment[73] for the interaction of two π-systems

$$\Delta E = 2\sum_{j}^{occ}\sum_{k}^{unocc}\frac{(\Sigma C_{rj}C_{sk}\beta_{rs})^2}{\alpha_j-\alpha_k} + 2\sum_{j}^{unocc}\sum_{k}^{occ}\frac{(\Sigma C_{rj}C_{sk}\beta_{rs})^2}{\alpha_k-\alpha_j} \qquad (23)$$

$$i.e.\ \Delta E = 2\left(\sum_{j}^{occ}\sum_{k}^{unocc} - \sum_{j}^{unocc}\sum_{k}^{occ}\frac{(\Sigma C_{rj}C_{sk}\beta_{rs})^2}{\alpha_j-\alpha_k}\right)$$

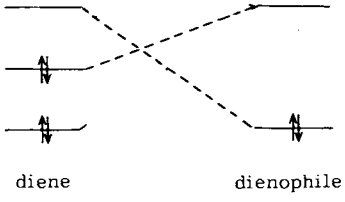


Fig. 22. Reaction of dienes with activated olefins.

From the relative positions of the orbitals, it follows that interactions of occupied orbitals of the diene with unoccupied levels of the dienophile are more important than the interactions of occupied dienophile levels with unoccupied diene orbitals[*]. The coefficients of polyene orbitals change in a regular way[**]. Thus for a chain of n atoms,

$$(C_1 \equiv C_n)_{\psi_{n+1}} > (C_1 \equiv C_n)_{\psi_n}$$

Considering the reaction of butadiene with ethylene

$$\Delta E = \frac{2(C_1' C_1^0 + C_4' C_2^0)^2 \beta_{rs}^2}{\alpha_1' - \alpha_2} \qquad (\alpha_1')\frac{(+)\,(-)}{C_1'\ \ C_4'}, \quad \frac{(+)\,(-)}{C_1^0\ \ C_2^0}(\alpha_2)$$

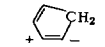
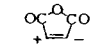
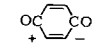
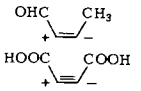
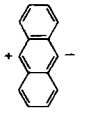
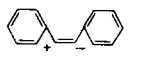
dienophile

$$+ \frac{2(C_1 C_1^0 + C_4 C_2^0)^2 \beta_{rs}^2}{\alpha_1 - \alpha_2} \qquad (\alpha_1)\frac{(+)\,(+)}{C_1\ \ C_4}$$

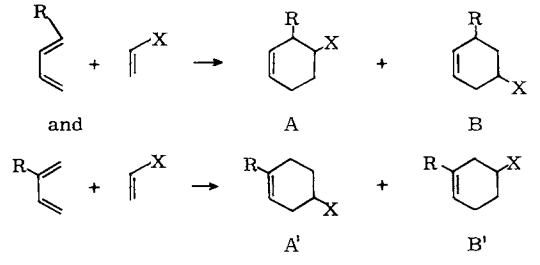
$$i.e.\ \Delta E \approx \frac{2(C_1' C_1^0 + C_4' C_2^0)^2 \beta_{rs}^2}{\alpha_1' - \alpha_2} \qquad \text{diene} \qquad (24)$$

The perturbation is thus determined mainly by the interaction of the highest occupied orbital of the diene with the lowest unoccupied orbital of the dienophile as postulated in the original paper by *Hoffman* and *Woodward*[69] and by *Fukui*[74]. The symmetry of the frontier orbitals of diene and dienophile are, in general, correct for concerted bond formation[74] (Table 4).

Table 4. Perturbation-determining frontier orbital in the reaction of dienes with dienophiles.

Frontier orbital of diene (HOMO)	Frontier orbital of dienophile (LUMO)
	
	
	
	
	

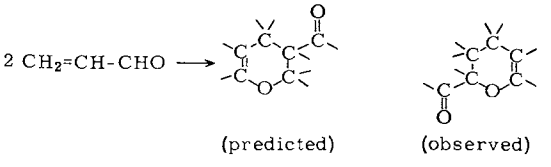
The perturbation equation has been used to predict the isomer ratios formed in the following reactions:



R = C_6H_5, CH_3; X = CN, CO_2CH_3, CHO, C_6H_5

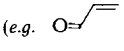
In all cases formation of isomer A (or A') is predicted; the result is in agreement with experimental findings, *e.g.* when $R = C_6H_5$, $X = CO_2CH_3$: $A \approx 90\%$; $A' \approx 80\%$.

In some cases, however, the incorrect isomer is predicted[75] *e.g.* in the selective dimerization of acrolein



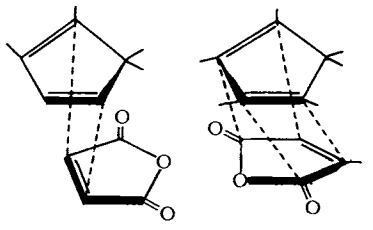
Here, the Coulomb term[*] in eq. 14 makes an important contribution and determines the isomer composition[76];

[*] 1,3 Dipolar additions can be treated in this way.
[**] This can readily be written in analytical form.

[*] According to *O. Eisenstein, J. M. Lefour,* and *Nguyen Trong Anh* (Chem. Commun. *1971*, 969), the regiospecificity is determined by interaction of the atoms with highest HOMO and LUMO coefficients (*e.g.* ).

there is some doubt, however, as to whether this and similar reactions are concerted or two stage processes[76a].

In addition, the stereochemistry of the product can be ascertained from the perturbation treatment. Thus cyclic reagents can give rise to *exo* or *endo* products, such as *e.g.* the reaction between cyclopentadiene and maleic anhydride (Fig. 23).



exo-Addition *endo*-Addition

Fig. 23. Cycloaddition of cyclopentadiene with maleic anhydride.

The preferential formation of the *endo* product is attributed to secondary interactions involving C2 and C3 atoms of the diene with the activating function of the dienophile (*e.g.* the carbonyl groups of maleic anhydride)[77].

Inclusion of these interactions leads to the perturbation energies[78] in Table 5.

Table 5. Perturbation energies of cycloadditions.

Diene	Dienophile	ΔE (kcal/mol) *endo*	*exo*
CPD	+ CPD	11.8	9.5
CPD	+ MA	18.9	14.2
CPDO	+ CPDO	41.7	29.2
CPDO	+ MA	20.6	13.2
CPD	+ CPDO	28.0	—
CPDO	+ CPD	21.8	—

CPD = cyclopentadiene, CPDO = cyclopentadienone, MA = maleic anhydride.

10. The Influence of Polarity

So far we have concentrated mainly on the reactions of non-polar π systems and molecules of weak polarity, *e.g.* radicals, where orbital interactions normally determine the course of the reaction. For polar molecules, the energy of Coulomb interaction (eq. (14)) may become important and Coulomb and orbital terms may be in opposition[12].

If a nucleophile is represented by a doubly filled atomic orbital ($C_{rs}=1.0$) eq. (14) becomes

$$\Delta E = q_r q_s \Gamma_{rs} + 2C_{sk}^2\beta_{rs}^2/(\alpha_j - \alpha_k) \qquad (14a)$$

For certain restricted series of reagents these two terms change in the same direction with a change in structure of the nucleophile. For example, consider the substitution of an electron attracting substituent A in an alkoxide ion

$$CH_3\text{-}O^{(-)} \qquad {}^{(\delta-)}A\text{-}CH_2\text{-}O^{(\Delta-)}$$

This has the effect of (i) reducing the formal negative charge on the nucleophile and (ii) reducing the energy of the "nucleophilic" orbital, (j), leading to decreased orbital interaction. Under these conditions the two nucleophiles show the same relative reactivity order to all electrophilic centers as required by the Brønsted relation (Section 3).

This is however not always the case, and the nucleophilic order may change with the nature of the electrophile[79]. This may be understood by comparing alkylation and acylation. The first term of eq. (14) is small for alkyl halides, and hence the reactivity order[80] follows the perturbation given by the second term, *e.g.* $I^- > Br^- > Cl^- > F^-$ (Fig. 24), *i.e.* it is *orbital controlled.*

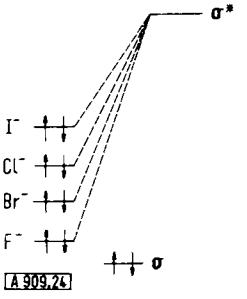


Fig. 24. Orbital interaction in alkyl halides.

On the other hand in acylation, the first term in eq. (14) is large in view of the high positive charge on the carbonyl carbon atom, and, although the orbital term is also increased, since a π* level is lower than a σ* level, the first term is dominant and leads to a reverse nucleophilic order[*], *i.e.* to *charge control*[12]. By also including the solvation energy term in the Hamiltonian operator, *Klopman*[81] was able to show (Table 6) that the nucleophilic order changes in a regular way with the change in the relative magnitude of α_j and α_k. (For simple nucleophiles α_j gives the effective electronegativity of the nucleophile, which is related to the Coulomb term.)

Table 6. Change in nucleophilic reactivity with the orbital energy of the electrophile.

	I^-	Br^-	Cl^-	F^-	HS^-	CN^-	OH^-
R_{HX}(Å)	1.60	1.41	1.27	0.92	1.34	1.06	0.96
$-2\beta_X$(eV)	3.16	3.60	4.10	4.48	4.0	3.8	4.50
$-\alpha_j$	8.31	9.22	9.94	12.18	8.59	8.78	10.45
$\Delta E(\alpha_k = -7\,eV)$	2.52	1.75	1.54	1.06	2.64	2.30	1.49
$\Delta E(\alpha_k = -5\,eV)$	1.07	0.98	0.97	0.82	1.25	1.17	1.01
$\Delta E(\alpha_k = +1\,eV)$	0.451	0.479	0.516	0.535	0.551	0.557	0.58

It should be noted that the relative magnitude of the two terms usually changes with the extent of interaction between the reactants, *i.e.* with the magnitude of the perturbation or the position of the transition state along the reaction path[18]. This is given quantitatively[**] by the

[*] This provides a theoretical basis for the concept of "hard" and "soft" acids and bases [82].

[**] Except in anomalous cases.

Brønsted coefficient, χ, which therefore changes in a regular way with the nucleophilic order. A striking example is β-elimination[16a,24] where the transition state structure may be E_1-like ($\chi \rightarrow 0$) or E_1CB-like ($\chi \rightarrow 1$), viz:

$$B: + CH_3\overset{(+)}{-}CH_2 + \overset{(-)}{X} \rightarrow B\cdots H\cdots CH_2{=}CH_2\cdots X \rightarrow \overset{(+)}{B}H + \overset{(-)}{C}H_2{-}CH_2X$$

E_1 $\qquad$ E_2 $\qquad$ E_1CB

increase of χ ⟶

increase of k_H/k_D ⟶ ⟵ increase of k_H/k_D

The relative reactivity of thioalkoxide to ethoxide ions decreases regularly[16b] with increase in χ, since the Coulomb term becomes more important in the transition state (Table 7).

Table 7. Change in nucleophilic reactivity with transition state structure for β-elimination.

	k_{RS^-}/k_{RO^-}	β
tert.-C_4H_9Cl	8.3	0.17
tert.-$C_4H_9S(CH_3)_2^+$	0.31	0.46
Cyclohexyl tosylate	7.0	0.27
Cyclohexyl chloride	0.73	0.39
DDT	7.1×10^{-5}	0.88

Other examples have been found, and it appears to be a general rule that a *change of transition state leading to an increase in both charge and orbital terms usually produces a change from orbital to charge control*[*]. We shall invoke this principle when dealing with "ambident reagents".

11. The α-Effect.

Some nucleophiles, *e.g.* HO_2^-, ClO^-, RS^-, NH_2OH, N_2H_4, and some oximes and hydroxamic acids are more reactive than predicted[83] by the appropriate Brønsted relation (see Section 3). This appears to be due to the lone pair of electrons adjacent to the nucleophilic atom[84]. If this has the correct orientation with respect to the lone pair of electrons which enter into covalent bond formation with an electrophile, the orbitals will split[85] according to eq. (6). Such splitting can be seen directly in the photoionization spectra[86], and is responsible for changes in ionization potential, polarizability, redox potential, and modified UV spectra[87].

Accordingly the (occupied) π* orbital interacts more strongly with an "electrophilic" orbital (σ*) than do the unperturbed electrons of a simple nucleophile[88] (Fig. 25); thus leading to an increased reactivity. This is however modified by the Coulombic term of eq. (14). In general the adjacent atom with lone pairs will be more electronegative than carbon or hydrogen and hence will exert a positive inductive effect. This tends to reduce the reactivity of the so-called "α-nucleophile", and in particular the interaction with a proton is so large as to outweigh the orbital splitting effects. This means that the reactivity change (*e.g.* HO_2^- and HO^-) is in the opposite direction to the pK_a change (H_2O_2 is a stronger acid than H_2O by *ca.* 4 pK_a units). Typical rate data for HO_2^- and HO^- are given in Table 8.

Table 8. Relative reactivity of hydroperoxide and hydroxide ions in aqueous solution.

	C_6H_5CN	$CH_3OOC{-}C_6H_4{-}NO_2$	$(RO)_2POF$	$C_6H_5CH_2Br$
$k_{HO_2^-}/k_{HO^-}$	10^5	10^3	2×10^2	≈50

In some cases, however, the conformation of the nucleophile is such as to minimize electron repulsion[84] and when the two orbitals in question are orthogonal, the splitting is zero[*]. Some examples are shown in Fig. 26 in the form of idealized Newman projections.

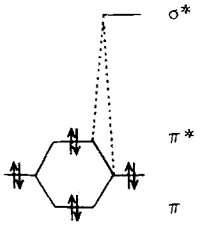
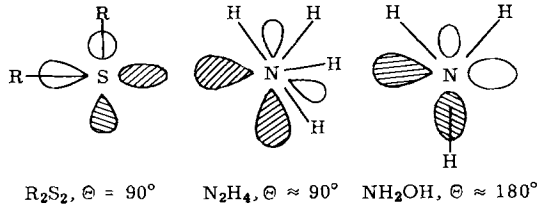


Fig. 25. Orbital interaction in the α-effect.



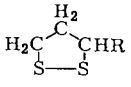
R_2S_2, Θ = 90° $\qquad$ N_2H_4, Θ ≈ 90° $\qquad$ NH_2OH, Θ ≈ 180°

Fig. 26. Conformations of nucleophiles with minimal electron repulsion.

[*] This is due to the large Coulombic term in polar bonds.

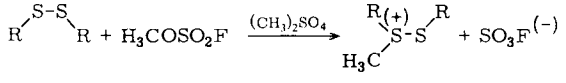
[*] As evidenced for instance by their normal refractivities, and PE spectra.

However, hydrazines and hydroxylamines do show enhanced reactivity[89] (*e.g.* in certain acylations and phosphorylations), and this has been ascribed to intramolecular base catalysis. These nucleophiles show "normal" reactivity[*] (*i.e.* follow the Brønsted rule) in alkylation[90] and general base catalysis in certain reactions[91]. Conformational factors may increase the overlap of the lone pairs, *e.g.* in trimethylene disulfide

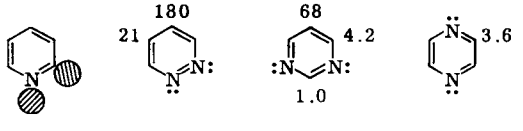


the dihedral angle is *ca.* 24°, and the sulfur atom is much more reactive, as in oxidation, to give the sulfone, than tetramethylene disulfide or non-cyclic disulfide[92].

We have shown[92a] that log $k \sim \cos^2\theta$, as required by eq. 8, for the alkylation of cyclic disulphides.



The influence of lone-pair interactions is also shown by the acidity of the hydrogen atoms of nitrogen heterocycles. Thus base catalyzed deuterium exchange[93] of pyridine shows that exchange at the 4 position is preferred, although Hückel charge densities suggest that the 2-position is the more acidic[94]. Extended Hückel calculations[95] suggest that the 2-carbanion is de-stabilized by lone-pair lone-pair repulsion.



Similarly the rate of base catalyzed deuterium exchange of diazenes can be explained readily by invoking lone pair repulsion between the electrons on nitrogen and the incipient carbanion[96].

Pyridazine and *iso*thiazole show α-effects in acylation and alkylation; pyrazine, pyrimidine and thiazole do not in reactions with 2,4-dinitrophenyl acetate[96a].

12. Positional Reactivity

The perturbation method is particularly useful in the prediction of the relative reactivity of two or more nucleophilic centers in a given nucleophile towards a range of electrophilic reagents. This is because the coefficients on atoms of the various orbitals of alternant hydrocarbons and their heteroatomic analogs usually change in a regular way. The influence of the heteroatom can be introduced as a perturbation as in the method of *Coulson* and *Longuet-Higgins*[97], which modifies the form of the wavefunction.

This may be illustrated graphically (Fig. 27) by reference to the allylic and enolate ions.

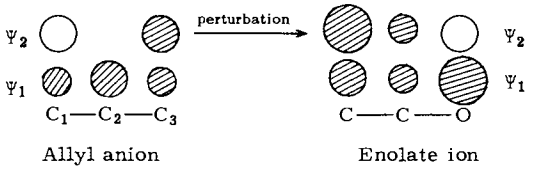
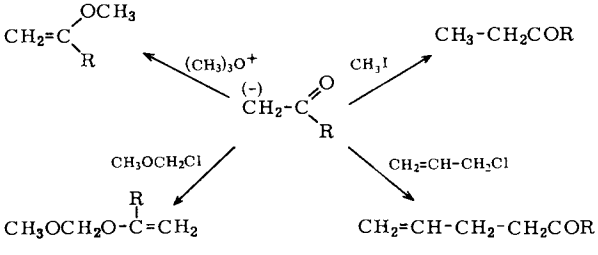


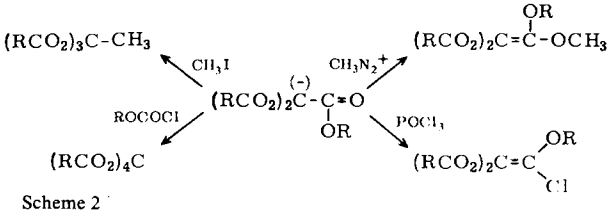
Fig. 27. Perturbation theoretical relationship between allyl anion and enolate ion.

The charges on the 1,3 carbon atoms of allylic anions are −0.5 e as the coefficients in the HOMO are equal. Substitution of oxygen for carbon atom 3 results in a concentration of electrons on oxygen in ψ_1, and a *reversal of the magnitude of the coefficients* on atoms 1 and 3 in orbital ψ_2. Thus $q_o > q_c$, but $C_c^f > C_o^f$ (C^f = frontier-orbital coefficient). Consequently when the Coulomb term is large, as in the reactions with cations—in particular protons and incipient carbonium ions (see Schemes 1 and 2)—the reaction becomes *charge controlled* with reaction on oxygen[*].

As the charge decreases the reaction becomes *orbital controlled*, and as shown by the reactions in Schemes 1 and 2, alkylation (and acylation) occurs on carbon.



Scheme 1.



Scheme 2

These are examples of the concept of *ambident reactivity* introduced in important papers by *Kornblum et al.*[98], who have shown that (for homogeneous reactions)[**] the

[*] See however *J. E. Dixon* and *T. C. Bruice*, J. Amer. Chem. Soc. *92*, 2052 (1972).

[*] NMR measurements show a concentration of charge on the oxygen atom of enolate ions (*G. J. Heiszwolf* and *H. Kloosterziel*, Rec. Trav. Chim. Pays Bas, *86*, 807, 1345 (1967). Extensive quantitative measurements have been reported by *A. L. Kurts*, *A. Marcias*, *I. P. Beletskaya*, and *O. A. Reutov* (Tetrahedron, *27*, 4759, 4769 (1971) and by *G. J. Heiszwolf* and *H. Kloosterziel*, Rec. Trav. Chim. Pays Bas *89*, 1153, 1217 (1970) on enolate ions and anions of imines.

[**] Heterogeneity introduces complications and specific explanations are required.

product composition changes in a regular way with structure, *e.g.*

$$Me\text{-}NO_2 \xleftarrow{MeI} O{=}N{=}O \xrightarrow{{}^tBuCl} {}^tBu\text{-}O\text{-}N{=}O$$

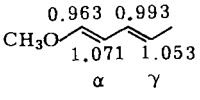
$$CH_3OC_6H_4CH_2\text{-}O\text{-}N{=}O \xleftarrow{CH_3OC_6H_4CH_2Cl} NO_2^- \xrightarrow{NO_2C_6H_4CH_2Cl} NO_2C_6H_4CH_2\text{-}NO_2$$

Again the S_N1 tendency leads to greater alkylation on oxygen. Rate determining protonation is almost invariably charge controlled in view of the large Coulombic term and relatively small orbital term, since the proton is strongly covalently bonded as H_3O^+ in solution. The perturbation thus involves a high energy σ^* orbital of the $H\text{—}\overset{+}{O}<$ bond. The pK_a however cannot be evaluated satisfactorily in this way, as the proton forms a complete covalent bond with the base. The perturbation then essentially involves an unoccupied 1s orbital, thus explaining the inadequacy of charge density in predicting the pK_a of certain aromatics[*].

The protonation of enolate ions and nitroalkane anions occurs initially on oxygen (kinetic control), and subsequently on carbon (thermodynamic control)[99].

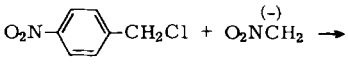
$$CH_2{=}\overset{+}{N}\text{-}\overset{O}{O}^{(-)} + H^+ \rightleftharpoons CH_2{=}\overset{+}{N}\text{-}\overset{\ddot{O}}{O}H \longrightarrow CH_3\text{-}NO_2$$

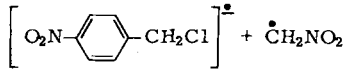
Likewise conjugated enol ethers undergo proton-deuterium exchange at the position of maximum charge density[100], *e.g.*

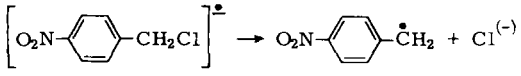


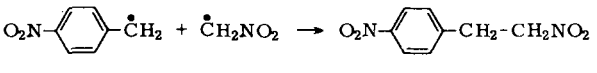
For a series of such ethers, $\log k_\alpha/k_\gamma \sim (q_\alpha - q_\gamma)$ and no correlation with localization energy is found.

On the other hand, interacting radicals are almost degenerate and subject to *orbital control*. This may explain the exclusive formation of C alkylated product in the reaction of nitroalkanes with *p*-nitrobenzyl bromide, which proceeds *via* a mechanism of the type[102]:



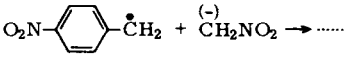






[*] Well known exceptions are encountered in protonation of heterocyclic bases [101].

The exact mechanism is not established, but radicals are certainly involved (probably in a chain reaction[102b], and the above explanation holds for other mechanisms, *e.g.*



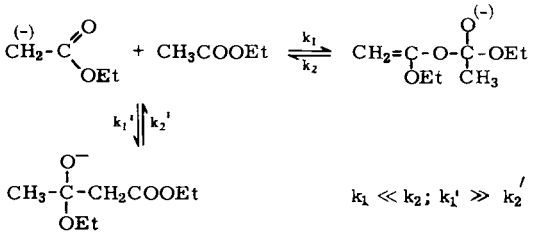
since the Coulomb term is negligible and the interacting orbitals are nearly degenerate.

These principles may be applied to the reactions of other conjugated nucleophiles (Table 9).

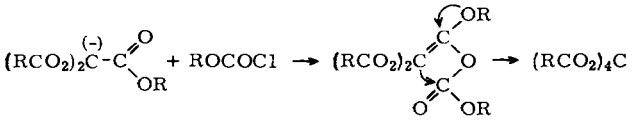
Table 9. Ambident activity of nucleophiles.

	CH_3OCH_2Cl	CH_3Cl	CH_3COCl	$(RO)_2POCl$
Orbital term	small	small	large	large
Charge term	large	small	large	large
$NCS^\ominus$	C—N	C—S	C—N	P—N
$R\overset{\ominus}{C}H\text{—}COR$	C—O	C—C	C—O	P—O
$R_2P(O)S^\ominus$	—	C—S	C—O	P—O

In general, a small charge with small orbital term leads to orbital control (*e.g.* alkylation), whereas a large charge with large orbital term leads to charge control (*e.g.* acylation and phosphorylation). The products however vary with the nature of the substrate and medium, and the interpretation is complicated by rearrangements and formation of products under thermodynamic control. Interesting examples of the relative importance of charge control and orbital control are found in the reaction of enolate ions with the phosphonium center[103], and the benzoylation of chelated 1,3 diketones[104] The Claisen condensation normally leads to *C*-acylated product, but this may be due to the influence of pre-equilibria, *e.g.*



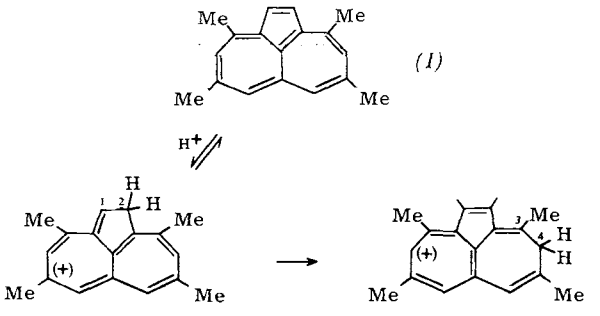
Similarly the formation of the fourfold acylated product in Scheme 2 could be formed by a rearrangement.



13. Aromatic Compounds

13.1. Charge Controlled Reactions

As the electron density on each carbon atom of an alternant hydrocarbon is unity, the Coulomb term of eq. (14) vanishes, and hence these reactions cannot be charge controlled. This is not the case for non-alternant hydrocarbons, and recently *Hasselbach*[105] has shown the first example of charge control in the protonation of *(1)* (Table 10). The kinetic product subsequently rearranges to give the thermodynamically stable product.



(1)

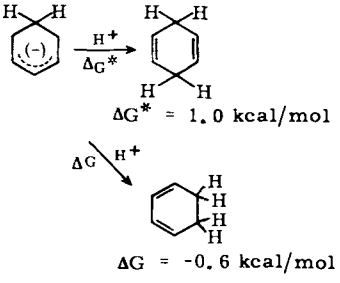
Such a behavior was predicted by *Brown*[62] who pointed out that the non-crossing rule is probably violated for non-alternants if the orders of q and ΔL (localization energy) differ.

Table 10. Parameters of charge controlled protonation.

$q_{1,2} = 1.125$	$q^f_{6,7} = 0.330$	$\Delta L_{6,7} = 1.875$
$q_{6,7} = 1.092$	$q^f_{4,9} = 0.276$	$\Delta L_{4,9} = 1.995$
$q_{4,9} = 1.088$	$q^f_{1,2} = 0.122$	$\Delta L_{1,2} = 2.014$

Streitwieser found similar results for aceheptylene[106].

The mechanism of the Birch reduction[107] of benzene involving the formation of a cyclopentadienyl anion has aroused much interest since the thermodynamically less stable 1,4-dihydrobenzene is formed.

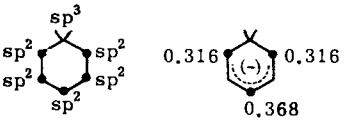


$\Delta G^* = 1.0$ kcal/mol

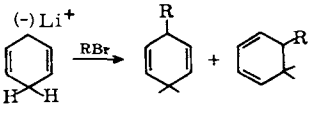
$\Delta G = -0.6$ kcal/mol

Simple Hückel calculations predict equal charge densities at positions 2 and 4[*], but when allowance is made for differences in electronegativities of these carbon atoms, SCF calculations give a higher charge density in the 4-position[107].

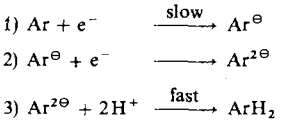
[*] In this case the charge densities and frontier electron densities are identical.



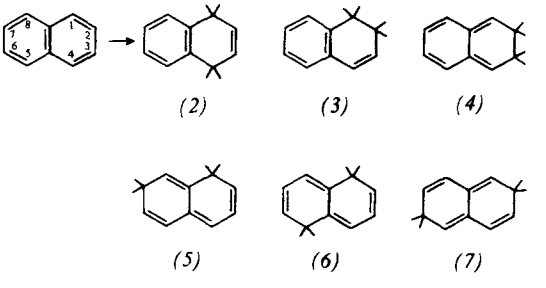
Similarly, alkylation gives a 3:1 mixture of 1,4 and 1,2 isomers[109]:



The products of polarographic reduction of polycyclic aromatics can be explained in a similar manner. The work of *Wawzonek* and *Latinen*[108] has established an irreversible mechanism for this reduction:



Here the addition of electrons to the lowest unoccupied level of the hydrocarbon is rate determining and hence the rate of reduction is related directly to the energy of this orbital. In the case of naphthalene there are six possible products of reduction. Compound *(3)* obviously has the highest resonance energy but this is not formed. The product is therefore determined by kinetic competition and since this involves the addition of protons to a dianion, the pertinent reaction is presumably charge controlled.



(2) *(3)* *(4)*

(5) *(6)* *(7)*

The charge density is given by the coefficients of the highest occupied orbital (HOMO) of the dianion[*], *i.e.*

$$\psi_6 = 0.4253(\varphi_1 + \varphi_4 - \varphi_5 - \varphi_8) - 0.2628(\varphi_2 + \varphi_3 - \varphi_6 - \varphi_7)$$

Thus

$$q_1 = q_4 = q_5 = q_8 = 0.181$$
$$q_2 = q_3 = q_6 = q_7 = 0.069$$

Hence only compounds *(2)* and *(6)* should be formed. Now the resonance energy of *(2)* is greater than that of *(6)* so that compound *(2)* is the normal product of reduction (Birch reduction also). It should be noted that

[*] Since the parent hydrocarbon is alternant and hence $q_r = 1.0$.

charge coefficients and frontier coefficients predict the same isomers in this case, since the charge distribution is given by the frontier orbital coefficients.

13.2. Charge and Orbital Control

In general however the reactions of aromatic species will be charge or orbital controlled in view of the extensive interaction with the π-system.

The wave functions are modified in a regular way by a heteroatom (or carbon atom of different hybridization, as in toluene) according to the rule of alternating coefficients[*]. Thus we shall be concerned with the *o/p* ratios in electrophilic substitution, which have not been explained unambiguously[**], and show that the perturbation treatment leads to a general electronic explanation. The charge densities (C_{rj}^2) on *o*- and *p*- carbon atoms of toluene (also for aniline, anisole *etc.*) can be represented diagrammatically (Fig. 28). Again the alternation leads to the conclusion that

$q_o > q_p$ but $q_p^f \gg q_o^f$

Thus strong perturbation (as measured by a large Brønsted coefficient, or a large reaction selectivity), should lead to exclusive *p*-substitution (as in Friedel Crafts acylation), weaker perturbation should lead to greater *o*-substitution.

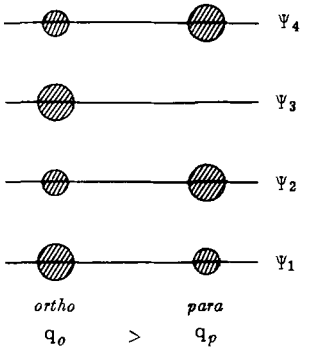


Fig. 28. Charge densities on the *o*- and *p*-carbon atoms in toluene.

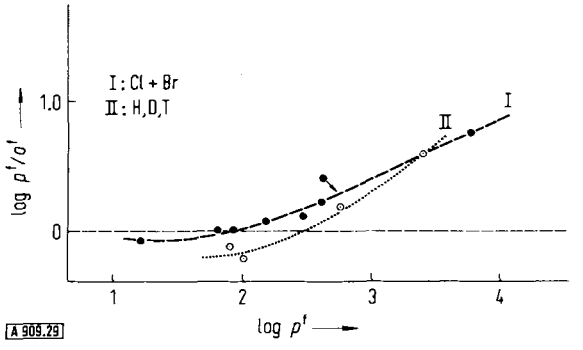


Fig. 29. Relationship between the *ortho-para* isomer ratio and selectivity (log p^f) for electrophilic substitution of toluene.

[*] For the benefit of prowling theoreticians, we acknowledge that this rule is not theoretically derived.

[**] *Norman et al.* [110] attributed high *o*-ratios to the charge distribution in the Wheland intermediate; *Kovacic* [111] has invoked specific *o*-group attractions.

The available experimental data[112] for toluene (in homogeneous solution) are in general agreement with these predictions. Thus in Fig. 29 two separate lines are obtained for (i) the deuteration and tritiation of toluene under various conditions, and (ii) for the reactions of Cl_2 and Br_2 in various media. It should be pointed out that the perturbation (eq. (14)) involves the resonance integral β for the incipient bond. This is the reason for the separate lines in Fig. 29. It is highly probable that the β values for C—Br and C—Cl bonds are similar[*].

In the cases of acylation, alkylation, and nitration a similar behavior is observed, *e.g.* o^f/p^f for nitration is *ca.* 1 when p^f is *ca.* 70. The influence of steric hindrance however appreciably reduces reaction at the *o*-position (as can be seen for example by considering the Friedel Crafts reaction of alkyl halides). *Olah*[29] has recently commented on the regular decrease in p^f/o^f with p^f for the reaction of substituted benzyl halides with toluene.

It is emphasized that the above treatment is an oversimplification of the process, and in particular all the orbitals $\psi_1 \rightarrow \psi_4$ should be considered. This leads to interesting results in the case of pyridine oxide, where calculations of the total perturbation energy (eq. (14)) with gradually changing values of $(\alpha_j - \alpha_k)$ show a change in reactivity from $C_2 \rightarrow C_4 \rightarrow C_3$. It is interesting to note that electrophilic substitution has been observed in these three positions with change in electrophile[113], the energy of the acceptor orbital of which probably increases in the following order[**]

$$Hg^{2+} < NO_2^+ < SO_3$$

Nucleophilic addition to π systems will now be considered. For example, Michael addition to α, β unsaturated ketones may be attributed to the large coefficient on the terminal carbon atom in the lowest unoccupied orbital (LUMO) ($C_3^2 = 0.435$; $C_1^2 = 0.303$ using $k=1$ and $h=1$)[***]. The charge densities are in the opposite direction however ($q_3^+ = 0.286$ $q_1^+ = 0.392$) and hence reactions involving

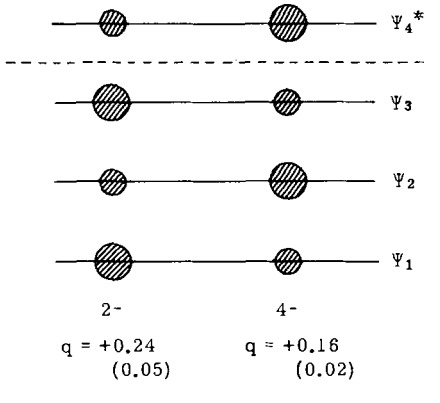


Fig. 30. Charge densities in positions 2 and 4 of pyridine.

[*] β also changes with selectivity, but in a regular way.

[**] Hg^{II} is a subgroup B metal, hence Coulombic forces are small; NO_2^+ has a relatively low lying π* orbital. SO_3 has high energy 3d orbitals.

[***] In the usual procedure $\beta_{C-X} = k\beta_{C=C}$; $\alpha_X = \alpha_C + h\beta$.

strong Coulombic interaction *e.g.* reduction with AlH_4^- or BH_4^- proceed at the carbonyl group.

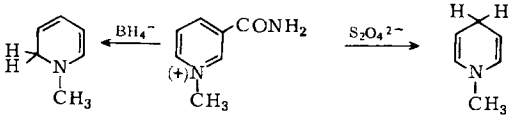
Similarly in the reduction of pyridine and pyridinium salts[114] the lowest unoccupied orbital is used in the initial stages of bond formation.

Figure 30 shows that the coefficients on C2 and C4 alternate, such that for the LUMO, $C_4^0 > C_2^0$, but $q_2^+ > q_4^+$. This means that reagents which interact strongly, react in position 4, whereas reagents which experience a large Coulombic interaction tend to react in position 2. Charge densities at the various atoms calculated by HMO and SCF methods are in the same order (Table 11)[115].

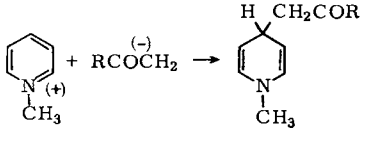
Table 11. π-Electron densities for pyridine.

	HMO	SCF [113]	VESCF [114]
q_1	1.180	1.100	1.107
q_2	0.943	0.950	0.952
q_3	0.992	1.010	1.004
q_4	0.950	0.980	0.981

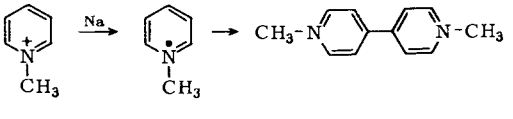
Experimentally[116] it is found that $S_2O_4^{2-}$, which forms a strong complex, reduces the 4-position, whereas BH_4^-, which cannot interact covalently, reduces the 2-position.



Similarly enolate ions which also form strong complexes and hence interact strongly with the HOMO, add at the 4-position[117].



The same considerations determine the almost exclusive formation of 4,4'-dipyridyl derivatives (*e.g.* "paraquat") by reduction *via* free radicals[118] (or radical anions).



Here there is no doubt that the maximum pertubation leads to coupling in the 4,4' positions. Similarly quinoline forms the 4,4' isomer and isoquinoline should form the 2,2' isomer. In both cases, however, total charge densities predict the same result.

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Structure and Function of Ferritin[**]

By Robert R. Crichton[*]

Ferritin is the major iron storage protein of mammals and consists of up to 4500 atoms of ferric iron surrounded by a shell of protein subunits. The protein component, apoferritin, consists of 24 identical polypeptide chains each of molecular weight 18500. The function of ferritin is to store iron in a soluble form from which it can be readily mobilized. Recent results concerning the structure of the protein are reported, and progress in the elucidation of the mechanisms whereby iron is introduced into apoferritin and released from ferritin is reviewed.

1. Introduction

"*Schmiedeberg*, the well known German pharmacologist, described in 1894 a protein substance which he called ferr*a*tin ... and contained 6% of iron and a variable quantity of phosphorus. Our efforts to isolate the iron rich component in a pure state from horse liver were not fruitful. It was not until we had chosen the spleen of the horse that we were able to prepare the pure substance. We have given to this new protein the name of ferr*i*tin, in memory of the ferr*a*tin of *Schmiedeberg*. On analysis ferritin contains 20% of Fe, 9.9% of N, and 0.9% of P. In the opinion of the author, ferritin must be a substance which serves as a depot for iron in the organism".

The isolation and crystallization of horse spleen ferritin thus described by *Laufberger*[1] in 1937 was the catalyst that led to recognition of the widespread distribution of this protein and to the establishment of its fundamental role in the storage of iron within the tissues and in the regulation of iron absorption from the intestine. In the present article the results of recent investigations on a number of selected aspects of the structure and function of ferritin will be considered.

2. Structure of Horse Spleen Ferritin

Although ferritins from a wide range of tissues and organisms have been studied, the most extensively characterized protein is still that from horse spleen. The present review will deal exclusively with horse spleen ferritin, and so in the text mention of ferritin implies this protein. The term apoferritin will be used to describe the iron-free protein, whether prepared from native ferritin by centrifugal techniques, or by chemical removal of the iron from ferritin. The demonstration that ferritins of differing structure occur within different tissues of the same species, that certain tumors contain atypical ferritins, and that the administration of iron either *in vivo* or *in vitro* causes stimulation of ferritin synthesis has been reviewed elsewhere[2].

2.1. Isolation and Gross Anatomy of Ferritin

Ferritin can be readily isolated from horse spleen by virtue of its stability at high temperature, ease of precipitation by 35% $(NH_4)_2SO_4$, and ready crystallization from 5% $CdSO_4$ solution. The isolation of the protein from other tissues and species presents a number of problems[3]. Ferritin consists of a shell of protein subunits surrounding a micelle of ferric hydroxide oxide phosphate. The iron can be removed by reduction with any suitable reducing agent, preferably in the presence of a suitable chelating agent to assist in removal of the Fe^{2+}. The original procedure described by *Granick*[4] involved $Na_2S_2O_3$ with α,α'-bipyridyl at pH 4.5. This suffers from the disadvantage that any molecular oxygen present causes the production of colloidal sulfur, which binds strongly to the protein and seriously interferes with subsequent investigations[5]. Accordingly we routinely remove the iron by treatment of ferritin with thioglycolic acid[6]. No precautions to exclude oxygen are necessary, and the thioglycolate functions both as reductant and chelator. Ascorbic acid at concentrations of 0.5–1.5 mol/l and pH values between 3 and 5 will also effectively remove iron from ferritin[6].

Apoferritin can be prepared from native ferritin solutions by centrifugation in an isopycnic density gradient[7], since native ferritin varies in its iron content from zero up to an estimated maximum of 4300 atoms/molecule[7] (Fig. 1). Whereas ferritin is inhomogeneous on account of its variable iron content, apoferritin is homogeneous, colorless, and can also be crystallized from 5% $CdSO_4$ solution[4]. It has the same electrophoretic mobility as ferritin

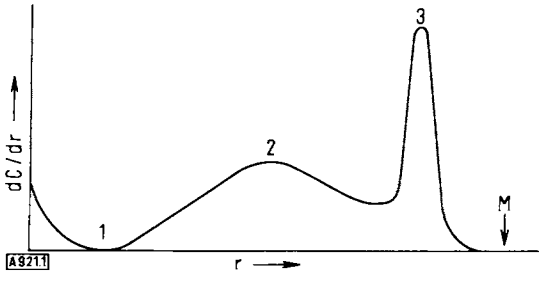

Fig. 1. Concentration gradient observed on sedimentation of native ferritin. The change in the concentration dC/dr is plotted against the distance from the center of rotation, r. Full ferritin (1) is at the bottom of the cell whilst iron-free apoferritin (3) is closest to the meniscus (M). Between these is partially filled ferritin of varying iron content (2).

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and is equally well precipitated by horse ferritin antiserum[8]. These data, together with electron microscopic studies[9], make it clear that the iron in ferritin is encapsulated within a protein shell.

2.2. Structure of the Micelle

Ferritin has a red-brown color on account of the large amount of ferric iron in the molecule (typically in unfractionated ferritin around 20% on a dry weight basis). The precise chemical nature of the iron core is not certain, but it seems that it contains all of the phosphorus of ferritin, and a possible composition $8\,Fe(OH)\cdot FeO(PO_3H_2)$ has been proposed[10,11]. The cores can be separated from the protein by precipitation with 1 N NaOH[12], and contain only 23% of the total phosphorus. The supernatant contains the protein and the remainder of the phosphorus, but it is not known whether this is bound to the protein or is present as free orthophosphate. Cores prepared in this way have the same X-ray diffraction pattern as intact ferritin[13]. Thus it has been concluded that the phosphate is not an essential structural component of the core, nor does it seem to contribute significantly to the diffraction pattern. Confirmation of this view is found in the observation that ferritins reconstituted from apoferritin by three different procedures in the absence of phosphate gave diffraction patterns similar to native ferritin. The cores released by alkali also retain much of their original shape as seen by electron microscopy[13]

A low angle X-ray scattering study[7] showed that at a resolution of 20 Å the core approximates to a single uniform density object of average diameter 75 Å. The core has sufficient density to be seen in the electron microscope without staining, and it was originally proposed that the iron was distributed in four electron-dense regions[9]. A more recent study using an electron microscope with an instrumental resolution better than 4 Å[14] indicates that no particular number of electron-dense groups is common. Both by direct viewing and by electron diffraction it was shown that, at least in the vacuum of the electron microscope, the iron oxide is present in the form of small crystallites, of varying number in different molecules, more or less randomly distributed within the protein shell.

Powder patterns typical of ferritin core preparations can be obtained from stationary single wet crystals of ferritin[13]. Both sharp spots, due to the protein crystal lattice, and very weak diffuse rings caused by the iron cores, can be seen simultaneously. The latter give no indication of preferred orientation with respect to the crystal lattice of the protein. This, together with the electron microscope study referred to above, supports the conclusion originally derived from the examination of X-ray diffraction photographs of single crystals of ferritin and apoferritin[15] that the atomic arrangement of the cores is not specifically related to the structure of the protein. This implies that either the protein does not have specific binding sites for the core, or else that if it does, the core material is bound to these sites randomly.

The X-ray diffraction pattern of the ferritin cores are typical of poorly crystalline material, with broad lines relatively weak in comparison to the background. The pattern is not identical with that of any known mineral but has some similarity to δ-ferric hydroxide oxide, and can be indexed on a hexagonal cell. A structure for the ferric hydroxide oxide of the ferritin core has been proposed by *Harrison et al.*[13] and also by *Towe* and *Bradley*[16]. The two structures have closely related unit cells.

The Mössbauer spectrum of ferritin at liquid N_2 temperatures and above consists of a quadrupole split line with an isomer shift with respect to stainless steel of 0.47–0.50 mm/s[17,18]. A six-line magnetic hyperfine spectrum is observed at low temperatures (5 °K) indicative of magnetic ordering. As the temperature is raised, the hyperfine spectrum is gradually replaced by the paramagnetic, quadrupole-split doublet spectrum. This superparamagnetism is thought to be characteristic of very fine magnetic particles[19].

The effective magnetic moment of ferritin was found to be 3.81–3.85 BM[10,20,21] and it was suggested that the reduced moment was due to transfer of two electrons from oxygen atoms to ferric atoms caused by the cation-anion-cation superexchange[20]. However, when a thorough field dependence study of the magnetization was carried out, a moment of 5.08 BM/iron was found[17]. The low value of the apparent moment shows that the ferritin particles are antiferromagnetic when behaving as superparamagnets.

2.3. Dissociation; Subunit and Oligomer Molecular Weight

The earliest determination of the molecular weight of apoferritin gave a value of 465 000[22]. It is clearly unlikely that such a molecule consists of a single polypeptide chain, and evidence for a subunit structure was obtained from X-ray diffraction studies and from chemical studies which are discussed below. The apoferritin molecule has a sedimentation coefficient of 17.6 S[22] and can be dissociated into subunits which sediment at 2–3 S by a number of techniques. Incubation of apoferritin at pH 12.6 results in dissociation into a 2.1 S component, but only to the extent of 50%[23]. However, treatment with 67% acetic acid at 0 °C leads to complete dissociation and the molecule remains dissociated on dialysis into 0.01 M glycine-HCl buffer, pH 3.0, and sediments at 2.7 S[24].

Dissociation of apoferritin and ferritin can be achieved by treatment with sodium dodecyl sulfate[23,25,26] and by the use of guanidine hydrochloride at concentrations of 5–6 M[27,28], although it has been recently reported that this latter process is strongly pH-dependent[29]. Urea, even at concentrations of 8 mol/l does not cause the protein to dissociate[23], although this process seems also to be pH-dependent[29]. We found that maleylation of the lysine residues of apoferritin[6] or their conversion to homoarginine residues[30] does not cause the protein to dissociate into subunits. It was previously reported that succinylation of the lysine residues caused dissociation[31]. Of the nine lysine residues per subunit only seven can be modified with maleic anhydride or with *O*-methylisourea, and eight of the nine arginine residues per subunit can be modified with cyclohexanedione. Only one out of the five

tyrosine residues per subunit can be nitrated with tetranitromethane[30].

Apoferritin can be dissociated into subunits by extremes of pH. We have analyzed this process by sedimentation velocity techniques and by gel filtration. The oligomer is stable beween pH 2.8 and 10.6. However, between pH 2.8–1.6 and 10.6–13.0 the oligomer gradually dissociates into subunits. The mid-points of the dissociation, at which equal amounts of 17 S and 2–3 S component can be detected in the ultracentrifuge, are respectively pH 2.16 and 11.62. When apoferritin is completely dissociated into subunits at pH 1.6 and then dialyzed against buffers of pH 1.8–5.0 a reassociation to oligomer is observed in the range pH 3.1–4.3, with the mid-point at pH 3.76[30]. Analysis of the dissociation and reassociation by gel filtration reveals not only monomeric subunits but also dimers and tetramers as intermediates: these intermediates were not observed by the sedimentation velocity techniques[30a]. UV difference spectroscopy of the dissociation process at low pH has established that the five tyrosines of the apoferritin subunit, which are buried in the interior of the molecule in the oligomer, become exposed to the solvent in the fully dissociated subunit. During the reassociation, they return to their original "buried" state[30].

The pH-dependence of protein denaturants such as guanidine hydrochloride and urea may reflect the importance of salt linkages in the quaternary structure. It is known that hydrophobic interactions play a major role in stabilizing the quaternary structure of oligomeric proteins and the effects of such reagents as guanidine hydrochloride and sodium dodecyl sulfate on the dissociation of apoferritin are consistent with such a role. Apoferritin has a relatively high content of hydrophobic amino acids, especially leucine (Table 1).

Table 1. Amino acid composition of apoferritin.

Amino acid residues	No of residues/ 18500 daltons	No of residues/ 23000 daltons
Cysteic acid	2.9	3.6
Aspartic acid	17.3	21.6
Threonine	5.5	6.9
Serine	9.0	11.3
Glutamic acid	23.9	29.9
Proline	2.8	3.5
Glycine	9.9	12.4
Alanine	14.0	17.5
Valine	7.0	8.8
Methionine	2.8	3.5
Isoleucine	3.5	4.3
Leucine	25.0	31.0
Tyrosine	5.0	6.2
Phenylalanine	7.3	9.0
Histidine	5.8	7.2
Lysine	8.7	10.8
Arginine	9.5	11.8
Tryptophan	2.1	2.6

The molecular weight of the apoferritin subunit was originally determined by sedimentation equilibrium studies with sodium dodecyl sulfate-dissociated protein[23]. A value of 25000–27000 was found on calculating the amount of detergent bound by equilibrium dialysis. We have redetermined the subunit molecular weight of apoferritin by polyacrylamide-gel electrophoresis in sodium dodecyl sulfate[25], gel filtration on calibrated columns of Sepharose 6B in 6 M guanidinium chloride, and sedimentation equilibrium studies on the acetic acid-dissociated protein, after dialysis into glycine buffer to remove bound acetic acid, and on the guanidine-dissociated protein[27]. In all cases we find a value of 18500. When the earlier data is recalculated assuming 1.4 g of detergent bound/g protein[32] a molecular weight of 18000–19000 is obtained[27]. Conformation of the value of 18500 for the subunit molecular weight has been reported from an American laboratory[28].

The apoferritin molecule has a tendency to aggregation which could easily lead to estimates of the molecular weight which are too high. However the use of UV optics in the analytical ultracentrifuge enables molecular-weight determination to be made by sedimentation equilibrium at concentrations of less than 1 mg/ml where there is no evidence of aggregation or other non-ideal behavior. Using a value of 0.731 for the partial specific volume ($\bar{v}$) a molecular weight of 443000 is obtained for the oligomer[33]. Results from a previous sedimentation diffusion study[22] and from X-ray diffraction[15] used a value of 0.747 for $\bar{v}$. With the new $\bar{v}$ these earlier estimates would reduce to 446000 and 443000 respectively. A value of 431000 was found by light scattering[34], and a recently published sedimentation equilibrium study using $\bar{v}$ of 0.732 gave 440000–465000[28]. We can conclude that the apoferritin molecule has a molecular weight of around 445000 and most probably consists of 24 subunits each of molecular weight 18500.

2.4. Primary Structure of Apoferritin

There are few things more boring than a progress report on determination of the primary structure of a protein without the actual sequence itself. The author is fully aware of this, but since it is germane to the arguments to be presented in Section 2.6, we will briefly discuss the present state of sequence studies which are proceeding currently in our laboratory in Berlin. It was established in the early sixties that the apoferritin molecule consisted of subunits and it was concluded on the basis of chemical[23,35,36] and subsequently of crystallographic evidence that the number of subunits was most probably 20. This evidence has recently been reviewed[27,37]. However, it is clear that on the basis of the present physicochemical evidence, the subunit molecular weight of apoferritin is 18500, not 23000–24000. A comparison of the two sets of data for the amino acid analysis of the protein (Table 1) reveals that there ought to be three methionine residues per subunit instead of four and hence following cleavage with CNBr we ought to find three new N-terminal groups. In fact after CNBr digestion we find equimolar amounts of three new end groups, namely, glutamic acid (or glutamine), isoleucine, and glycine[38]. Chromatography of the CNBr digests leads to the isolation of four peptides[39–42] which have amino acid compositions[38,42] whose sum closely corresponds to the amino acid composition of the apoferritin subunit. The molecular weights of these peptides can be readily estimated by chromatography on the same

Sepharose 6B column in 6 M guanidinium chloride as was used for determination of the subunit molecular weight of the protein, and it can be shown that the sum of their molecular weights is in good agreement with the subunit molecular weight[43].

Fingerprinting of tryptic digests of apoferritin reveals 25 peptides[5,35], rather more than would be predicted from the amino acid analysis (Table 1). However, in the course of our sequence studies we have already found several peptides which are the products of partial tryptic digestion, and in one case of non-tryptic digestion[44], which accounts for our finding more tryptic peptides than expected. The N-terminal pentapeptide and C-terminal octapeptide sequences of apoferritin have been determined[45,46]. Determination of the sequence of the tryptic peptides and the CNBr peptides is proceeding steadily.

It has been suggested that apoferritin is inhomogeneous since a heterogeneous pattern of bands has been observed on isoelectric focusing of ferritin and apoferritin in polyacrylamide gels and in sucrose density gradients[47,48]. There is, however, good reason to doubt whether the appearance of multiple bands is necessarily an indication of heterogeneity[49], and it seems that in the case of horse spleen ferritin the apparent microheterogeneity may be an artifact[50,51]. It has also been reported[28] that in dissociating solvents two lower molecular weight components are present which together account for some 10% of the total protein. We have found no evidence for such low molecular weight components under dissociating conditions[27].

2.5. Secondary and Tertiary Structure of Ferritin and Apoferritin

Analysis of ferritin by optical rotatory dispersion (ORD) and circular dichroism (CD) reveals that the content of α-helix is about 50%[52,53]. The spectra obtained are independent of the iron content of the ferritin. Chemical reduction of ferritin to give apoferritin produces a pronounced increase in secondary structure[52,53] as can be seen from the spectra presented in Figure 2. This is in marked contrast to the observations from X-ray crystallographic investigations. Not only does chemically prepared apoferritin crystallize in a form isomorphous with one form of ferritin[15], it has also been found that at low resolution no differences can be detected in the intensities of reflections due to the protein for ferritins of varying iron content and for apoferritin[54] which would indicate that the protein conformation is essentially unchanged. It has been recently reported that native apoferritin prepared by density gradient centrifugation has the same dichroic spectrum as ferritin[29].

Apoferritin is digested more rapidly and to a greater extent by trypsin, chymotrypsin, and subtilisin than is ferritin[5,55,56]. Pepsin and cathepsin D however digest both proteins equally well at pH 3.0, a fact that can be explained by the relatively non-specific nature of these two enzymes. With pepsin at pH 2.5, apoferritin is digested much more effectively than ferritin, and it was suggested

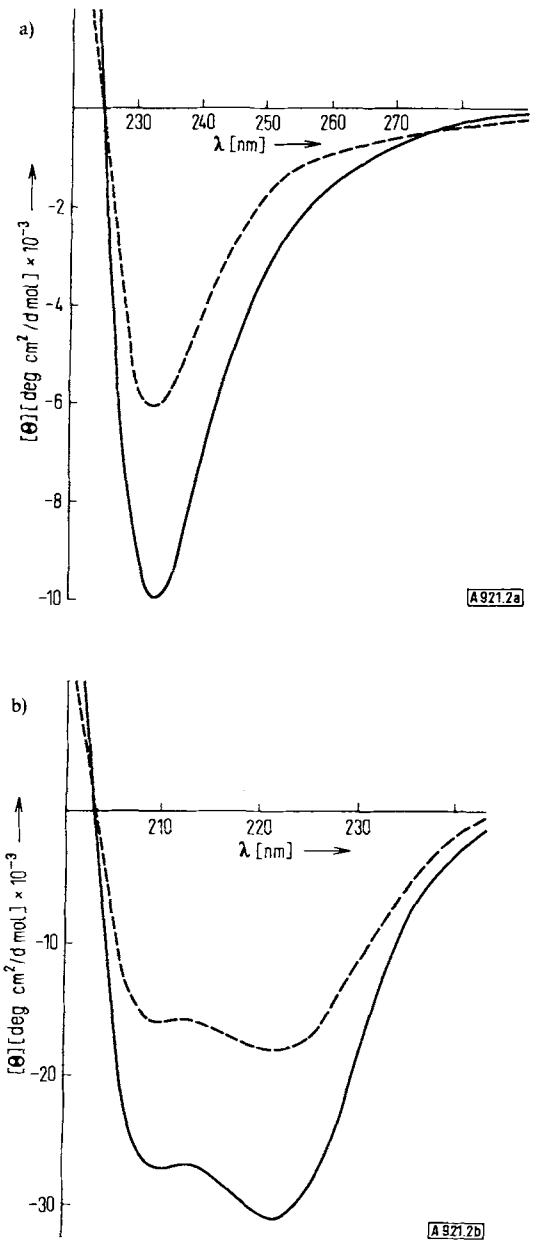

Fig. 2. ORD (a) and CD (b) spectra of ferritin (----) and apoferritin, prepared by reduction with thioglycolate (—). The depths of the trough at 233 nm in (a) and at 222 and 208 nm in (b) are a measure of the content of secondary structure present [52].

that this might reflect a partial unfolding of the apoferritin structure at low pH. An analysis of the effect of pH on the conformation of both proteins using ORD and CD revealed marked changes in the spectra of both proteins in the pH range of 3.1–2.2 which are consistent with a loss of about 10% of their ordered structure[52]. In the case of apoferritin (Fig. 3) marked changes in the near-UV dichroic spectrum were seen which suggest that the environment of the tyrosine and tryptophan residues of the protein changes considerably. The effect of protein denaturants on the secondary structure has been investigated[29] and it was shown that in 7 M guanidinium chloride, pH 7.5, complete disruption of helical segments occurred in ferritin and the protein was broken down into subunits. In contrast, under these conditions little change was seen in the dichroic spectrum of apoferritin. However,

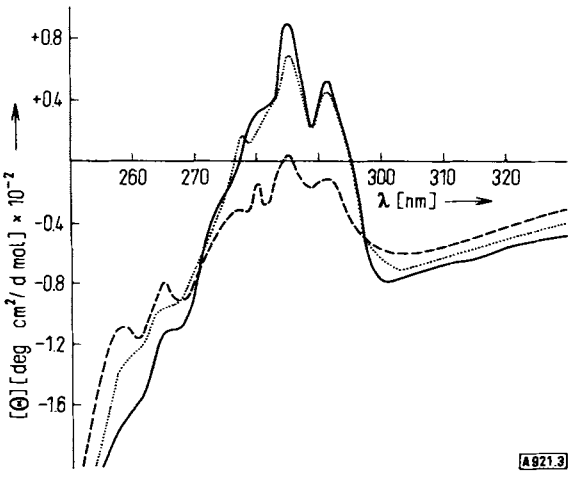

Fig. 3. CD spectra of apoferritin in citrate buffers: (——) at pH 3.11; (-----) at pH 2.80; (— —) at pH 2.50 [52].

at pH 4.5 apoferritin was also dissociated into subunits and unfolded in 7 M guanidinium chloride. Analogous effects were found with 10 M urea, where the native three-dimensional structure of ferritin and apoferritin was unaffected at pH 5.0–8.0 but was disrupted at lower pH values. The optical rotatory properties of ferritin at 233 nm in several organic solvents were similar to the rotations in aqueous solutions[53]. Thus it seems that the disruption of hydrophobic interactions does not induce additional α-helix formation.

2.6. Quaternary Structure of Apoferritin

Early X-ray powder photographs[57] indicated that ferritin and apoferritin were cubic and isomorphous. It was subsequently found by *Hodgkin*[58] and by *Cowan*[59] that single crystals of ferritin are orthorhombic, not cubic, wet unit cell dimensions being $a=130$ Å, $b=130$ Å, $c=184$ Å. The space group $P2_12_12_1$ was derived but it was subsequently concluded that this was not the true space group. A reinvestigation of apoferritin and two crystalline forms of ferritin, A and B[15], showed that all three crystals had identical lattice repeats: wet crystals of apoferritin and ferritin B were face-centered cubic with $a=184$ Å, while ferritin A was pseudocubic, and was truly face centered on only one face. The lattice of ferritin A could be described in terms of an orthorhombic cell with identical dimensions to those found previously. None of the space groups was determined unequivocally from the X-ray data, but it was concluded that the space group of apoferritin was probably F 432, the unit cell containing four molecules. In this case each molecule would have point group symmetry 432 and hence be composed of 24 n subunits, where n is an integer. A possible molecular structure was suggested consisting of 24 subunits situated at the vertices of a snub cube (Fig. 4).

In further investigations of this same cubic form[60] the X-ray photographs were found to contain a mixture of both sharp reflections extending to spacings of 1.0–1.4 Å, and diffuse streaks, characteristic of a structure having "ordered disorder". The existence of this non-uniform diffuse background was interpreted as indicating that although the unit cells repeat with geometric regularity, the internal arrangement was not the same for every unit cell. This situation could readily be produced by nearly

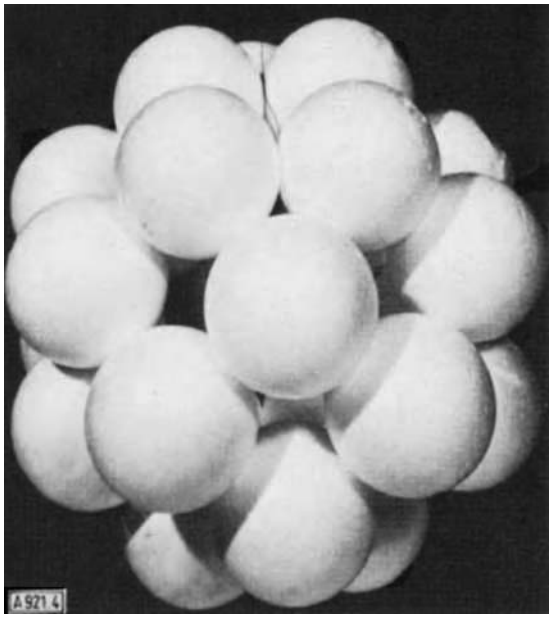

Fig. 4. Photograph of a possible spatial arrangement for a 24-subunit model. The subunits are situated at the vertices of a snub cube ({100} with {111} and {110}). The model shows a rhombohedral-dodecahedral face at the top and a cubic face standing on an apex at the front.

spherical molecules occupying equivalent lattice positions, but not all having the same orientations at corresponding positions of neighboring unit cells. Specifically it was proposed that the apparent 432 symmetry and the diffuse background could be accounted for by molecules with point group symmetry lower than 432 lying on the lattice points, but having several orientations such that the crystal symmetry was produced statistically.

The possibility that apoferritin molecules have 532 symmetry, or pseudo-532 symmetry was suggested by the rather strong intensities near the directions of the non-crystallographic five-fold axes and apparently convincing X-ray diffraction evidence for this pseudo-icosohedral symmetry together with the chemical and physico-chemical data discussed earlier led to the proposal that apoferritin consisted of twenty subunits situated at the vertices of a pentagonal dodecahedron with a small central hole in each pentagonal face. It was noted that certain features of the diffuse parts of the X-ray diffraction pattern were also consistent with this model.

It is clear from the data on the subunit and oligomer molecular weight presented above that a 20 subunit model is no longer likely for apoferritin. Indeed, as has been recently pointed out, the chemical and physico-chemical evidence for the existence of eicosameric structures in general is rather weak[37]. The problem of an eicosameric structure is that the subunits cannot all occupy equivalent positions in the structure, so that there must either be at least two different kinds of subunit, or else the same subunit

must be able to exist in two distinct conformations within the one quaternary structure[37,61]. As we have seen above, no evidence for the existence of more than one type of subunit has been forthcoming to date.

A 24-subunit structure would now seem to be most likely for apoferritin, although the exact arrangement of the subunits must await a more detailed X-ray analysis. *Harrison*'s original suggestion of a structure with 24 subunits distributed at the vertices of a snub cube[15] (Fig. 4) possesses some of the features which would be expected from a structure having icosohedral symmetry. Thus, for example, it gives strong intensities near the non-crystallographic five-fold axis of molecules with 532 symmetry.

3. Function of Ferritin

The principal function of ferritin is to serve as an intracellular iron storage depot particularly in spleen, liver, and bone marrow, in which excess iron can be deposited and from which iron can be mobilized when required. Tissue ferritin is in dynamic equilibrium with plasma iron: the iron in plasma is transported bound to transferrin, a β_1-globulin which has two binding sites, each capable of carrying one atom of ferric iron[62]. It has been demonstrated that transferrin binds to specific receptor sites on the cell membranes of maturing reticulocytes[63,64], and there is considerable evidence that ferritin iron in reticulocytes is utilized for hemoglobin synthesis[65,66]. Ferritin is also found in the mucosal cells of the small intestine and the possibility that it plays a role in the regulation of iron absorption from the intestine has been current for some time. It seems likely that it acts as an iron "curtain", trapping excess iron within the mucosal cell, and so ensuring that it is not absorbed but is lost when the mucosal cell is shed at the end of its life span.

3.1. *In Vitro* Studies on Ferritin Formation

Preliminary investigations showed that incubation of apoferritin in HCO_3^- buffer at pH 7 and 4–6 °C gave a product on air oxidation which could be crystallized with $CdSO_4$ and had an N:Fe ratio of 2.4:1[67]. The importance of this contribution was that it enabled a simple redox model for ferritin formation to be formulated:

$$\text{apoferritin} + Fe^{2+} + O_2 \rightarrow \text{ferritin}$$

It was subsequently reported that oxidation of ferrous ammonium sulfate in the presence of apoferritin either with O_2 in hydrogen carbonate buffer pH 6.8–8.0, with potassium iodate in sodium thiosulfate at pH 5.4–7.4, or with O_2 in imidazole buffer pH 6.7–7.0 gave a product which had the usual red-brown color of ferritin, had a sedimentation coefficient considerably larger than apoferritin, could be seen to have a dense core in the electron microscope, and had an X-ray diffraction pattern similar to native ferritin. In the absence of apoferritin, oxidation led respectively to the formation of α-ferric hydroxide oxide, γ-ferric hydroxide oxide, and a third unidentified product[13]. It was also noted that apoferritin appeared to affect the rate of oxidation of Fe^{2+}

An elaboration of this model was proposed by *Niederer*[68] who postulated that small molecules and ions could penetrate to the interior of the apoferritin molecule through holes in the protein shell. On the inner surface he suggested that apoferritin has active sites which could catalyze the oxidation of Fe^{2+}. The nascent ferric ions would readily form an intramolecular precipitate, which would eventually be too big to escape (Fig. 5).

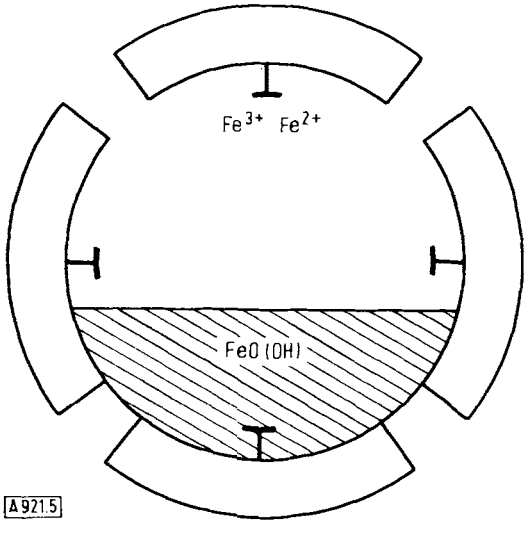

Fig. 5. Model for the formation of ferritin. Ferrous iron is oxidized to the ferric form by a suitable electron acceptor in a reaction catalyzed by active sites on the apoferritin subunits. The ferric hydroxide oxide forms a micelle which eventually becomes too large to escape from the protein shell.

As supporting evidence for this hypothesis it was shown that apoferritin stimulated the oxidation of Fe^{2+}. Treatment of apoferritin with formaldehyde and β-propiolactone, which react with amino groups and histidine residues, and with bromoacetate, a weak histidine alkylating agent, inhibited the iron uptake. Iodoacetamide and tetrazolediazonium chloride were reported to have no effect and Zn^{2+}, which is known to inhibit the *in vivo* formation of ferritin[69], inhibited the reaction strongly.

This process has been intensively studied both in our laboratory in Berlin and by *Harrison* and her colleagues in Sheffield. It has been reported[70] using potassium iodate as oxidant together with thiosulfate in imidazole buffer, pH 7.4, that the kinetics of iron uptake by apoferritin are complex. Apoferritin has a catalytic effect, as does bovine serum albumin, although the product formed is not the same as with apoferritin. We have found that at lower pH values using O_2 as oxidant, normal Michaelis-Menten kinetics are observed and the catalytic effect of other proteins such as lysozyme and bovine serum albumin is practically nil[71]. Carboxymethylation of two cysteine

residues and one histidine residue in each subunit leads to complete loss of catalytic activity[71].

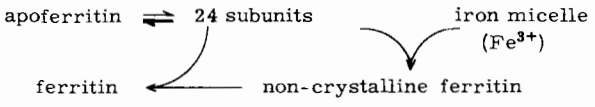

Fig. 6. Formation of ferritin from iron cores and apoferritin subunits. An equilibrium is postulated between apoferritin and its subunits. Ferric iron chelates hydrolyze and polymerize to give iron micelles, which cause a shift in this equilibrium by associating with subunits to form non-crystalline ferritin. This intermediate, lacking the complete protein shell, is rapidly converted to crystallizable ferritin.

Saltman et al.[72] have proposed an alternative model for formation of ferritin, which assumes the assembly of apoferritin subunits around a preformed iron micelle (Fig. 6). It is argued[73] that the chemistry of ferric chelates such as ferric fructose, ferric citrate, and ferric hydroxide nitrate in aqueous solutions is dominated by a tendency to hydrolyze and polymerize, giving soluble micelles which have approximately the same size as the core of full ferritin (70 Å). In the case of ferric hydroxide nitrate[74], the polymer, which has the approximate composition $Fe_4O_3(OH)_4(NO_3)_2$, has magnetic and Mössbauer properties which are very closely similar to those of ferritin. The results of an experiment in which an excess of apoferritin was incubated for various time intervals with the non-crystallizable fraction of ferritin, and the product crystallized from cadmium sulfate solution, showed that in 45 min it was possible to recover 100% of the iron originally present in non-crystalline ferritin as crystalline ferritin. This, together with electron microscopic evidence, is presented as support for the view that non-crystalline ferritin consists of ferritin molecules that lack the full complement of protein subunits, and implies that the presence of the iron micelle causes apoferritin to dissociate into subunits, which can then assemble around the micelle to give ferritin[72]. A recent preliminary report indicates that when an acidic solution of apoferritin subunits is added to natural polymeric iron cores isolated from ferritin, or to various synthetic polymers of ferric nitrate, ferric citrate, ferric fructose, and ferric-ATP, and rapidly neutralized, a product is formed which resembles ferritin in its elemental composition, electrophoretic and sedimentation behavior, and its appearance in the electron microscope[75].

A number of objections to the chelate model have been presented[76]. In the first place the observation that non-crystalline ferritin is deficient in protein subunits is at variance with observations of *Farrant*[9] who found ferritin and non-crystalline ferritin to be identical in electron micrographs. Non-crystalline ferritin has the same Fe:N ratio as the crystalline ferritin from which it was prepared[72] which leads one to conclude that if it contains incomplete protein shells, it must also contain free subunits. Indeed, the model assumes that apoferritin molecules are in equilibrium with the subunits.

There is at present no evidence for the dissociation of apoferritin into subunits under physiological conditions. According to the hypothesis presented in Figure 6, only two intermediates in the formation of ferritin should exist: iron-free apoferritin, and ferritin with the full complement of iron. However in experiments on the biosynthesis of ferritin induced by administration of iron, it was found using [^{14}C]leucine that radioactivity appeared first in iron-poor ferritin, and only after a relatively long period in iron-rich ferritin[77,78]. From this, one would conclude that the newly synthesized apoferritin was gradually filled with iron. *Niederer*[68] has pointed out that if one assumes that iron stabilizes ferritin so that subunit dissociation is very slow from iron rich ferritin by comparison with iron-poor ferritin or apoferritin, then newly-synthesized apoferritin would be incorporated into iron-poor ferritin present in the pre-existing liver ferritin pool rather than into iron-rich ferritin. He briefly reviews results which show that there is a gradual uptake of iron by apoferritin when the product is analyzed by isopycnic centrifugation in an urografin gradient[68]. This leads him to reject the chelate model but he neglects to note that the conditions of iron uptake used by him (see above) are such that the micellar aggregates found by *Pape et al.*[72] would not be formed. It can therefore be concluded that although there have been many criticisms of the chelate model, none of these is completely unequivocal, and the model cannot be excluded on the basis of the present evidence.

3.2. Mobilization of Iron from Ferritin

As was pointed out earlier[4], reduction of the ferric iron of ferritin to the ferrous form can liberate iron from the protein. *Bielig* and *Bayer*[79] showed that it was possible to mobilize iron from ferritin by the use of biological reducing agents such as ascorbate, glutathione, and NADH. However, the rates of mobilization, even with high concentrations of these reducing agents, are very low. In the search for a physiological redox system *Mazur et al.*[80] suggested that xanthine oxidase was responsible for ferritin iron reduction and mobilization in the liver. Such a role for xanthine oxidase had been proposed earlier by *Tanaka*[81], who found that the magnetic susceptibility of a ferritin solution slowly increased on treatment with xanthine oxidase and methylene blue and with reduced diaphorase. The observation that a patient with hemochromatosis, an inherited condition in which there is excessive iron storage, excreted xanthine in the urine, and had a markedly reduced level of liver xanthine oxidase led *Ayzvasian*[82] to propose the linked reduction of ferritin iron with the oxidation of xanthine and hypoxanthine, as outlined in Figure 7. The site for reduction of ferritin iron

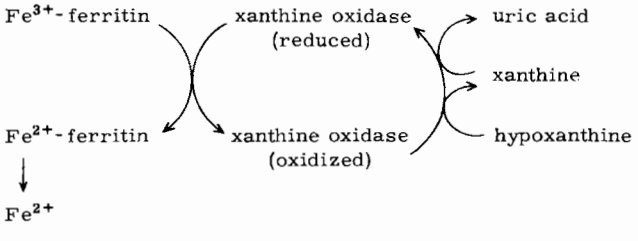

Fig. 7. The possible role of xanthine oxidase in the mobilization of iron from ferritin.

was thought to be the non-heme iron of xanthine oxidase[80]. However, several compounds such as allopurinol (4-hydroxypyrazolo[3,4-*d*]pyrimidine) which severely inhibit xanthine oxidase have little or no effect on iron metabolism[83].

The mobilization of iron from ferritin at rates of physiological significance can be accomplished by using specific low molecular weight chelating agents in the absence of reducing agents[84]. However, the most satisfactory chelating agent used in this study, nitrilotriacetate, is certainly not likely to have any physiological role. Whether a suitable cellular metabolite could function as effectively in non-reductive mobilization of ferritin iron remains to be established.

The possibility that physiologically available reducing or chelating agents might mobilize ferritin iron has recently been tested by us. We find that with the exception of ascorbate at concentrations greater than 200 mM and pH values lower than 5 and cysteine at concentrations greater than 100 mM none of the agents which we have examined either alone or in combination with other reductants or chelators is able to release iron from ferritin at rates which would be significant in the mammalian cell. The same is true for xanthine oxidase, which, in our hands, does not mobilize ferritin iron at all *in vitro*[6].

A specific enzyme activity has recently been found in mammalian liver homogenates, and partially purified by CM-Sephadex chromatography and ultracentrifugation which reductively mobilizes ferritin iron. The enzyme requires NADH and FMN for reduction of ferritin-bound Fe^{3+} to free Fe^{2+} presumably by transfer of electrons from NADH to ferritin. The reaction is reported to be inhibited by O_2, but not by allopurinol, which suggests that the enzyme is not liver xanthine oxidase. The enzyme is very heat-labile and has a pH optimum of 7.2–7.4. Hypoxanthine, succinate, ethanol, and glucose are not effective as electron donors. Preliminary ultracentrifugal studies suggest that the enzyme, for which the name ferriductase is proposed, is located mainly in the soluble fraction of the cell[85].

3.3. Iron Transfer between Ferritin and Transferrin

Transfer of iron from ferritin to transferrin across a semipermeable membrane was demonstrated by *Bielig* and *Bayer* to require ascorbic acid[79]. In the same year it was demonstrated[86] that ferritin containing small amounts of ferrous iron and free SH groups in liver slices could transfer iron to transferrin. It was subsequently found that ATP was specifically required for transfer of iron from transferrin to ferritin by liver slices and homogenates[87]. In a more detailed study using a model system in which the transfer of ^{59}Fe from transferrin to ferritin across a semipermeable membrane was measured, it was established that iron transfer required the presence of both reducing agents and chelating agents[88]. ATP was shown to act as a chelating agent, and not as a source of energy. The process of iron transfer from transferrin to ferritin was thus formulated as involving reduction, chelation, and oxidation as outlined in Figure 8. No specific compound was required

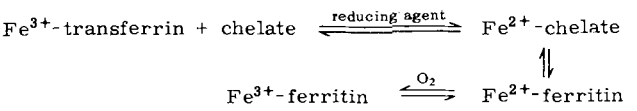

Fig. 8. Model for iron transfer from transferrin to ferritin. Transferrin-bound ferric iron is reduced and chelated, and the ferrous chelate then transfers its iron to ferritin. The ferrous iron is oxidized to the ferric form by molecular O_2.

as chelator, and a number of biologically available chelating agents such as sugars, ATP, ADP, and AMP were found to be effective.

Of the reducing agents that were examined, ascorbate was by far the best. The iron content of the ferritin and transferrin used regulated the amount of transfer that was observed. Transferrin that was 50% saturated or less did not transfer iron. Ferritin took up most iron when it was about 50% saturated with iron. Preliminary experiments have shown that when apotransferrin is dialyzed against ferritin in the presence of reducing and chelating agents, the reverse transfer continues until the transferrin is 40% saturated with iron[89]. Thus both the forward and reverse reactions can be explained by the mechanism outlined in Figure 8.

4. Outlook

From the results which have been briefly reviewed here it can be seen that the study of the structure and function of ferritin is rapidly reaching a phase of intense interest and enormous activity. The establishment of the primary structure of the horse spleen protein together with the identification of those parts of the primary structure which are involved in catalysis of the oxidation of ferrous iron should give great incentive to a reinvestigation of the three-dimensional structure of the protein.

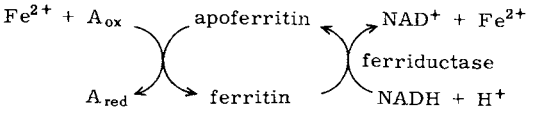

Fig. 9. The insertion of iron into apoferritin from Fe^{2+} is catalyzed by the protein itself in the presence of a suitable oxidizing agent A. Mobilization of iron as Fe^{2+} from ferritin is brought about by an enzyme designated as ferriductase which is NADH-dependent.

The possibility, outlined in Figure 9, that a complete redox system is involved both in insertion of iron into ferritin and in its mobilization from ferritin, opens the way to a detailed analysis of the regulation of these two pathways, and hence as our understanding of these processes grows, to a more rational therapeutic approach to disorders of iron storage. This is particularly crucial at a time when increasing use of transfusion therapy to combat anemia is leading to an ever-increasing number of cases of secondary iron overload (transfusion siderosis). If, as seems increasingly likely, the ferritin iron in reticulocytes is utilized for hemoglobin synthesis[65,66], it becomes even more important to understand the nature of the factors that regulate the dynamic equilibrium between the introduction of iron into ferritin and its mobilization from the

storage form. And if the mechanisms for iron introduction and removal from ferritin involve oxidation and reduction respectively, there can be little doubt that somewhere within the cell a system must exist for oxidation of Fe^{2+} to Fe^{3+} prior to, or simultaneously with, the uptake of iron by transferrin at the cell surface. This system must also be capable of reduction of the ferric iron of transferrin and its delivery within the cell as Fe^{2+}. It is tempting to speculate that the carrier system, which may or may not be enzymic in nature, is located within the cell membrane, acting as a shuttle between the outer and inner surface in the same way as *Margoliash et al.*[90] have proposed for cytochrome C in the inner mitochondrial membrane. The elucidation of this pathway will give us yet more insight into the regulation of the many processes that pass under the general heading of iron methabolism, and into the one small corner with which we have concerned ourselves here.

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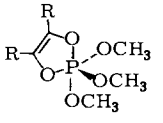
Five-Membered Cyclic Acyl Phosphates, a New Class of Extremely Reactive Phosphorylating Agents

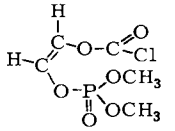
By *Fausto Ramirez, Stephen Glaser, Peter Stern, Paul D. Gillespie,* and *Ivar Ugi*[*]

In the synthesis of phosphate esters, including the polynucleotides, only phosphoryl halides and acyclic mixed anhydrides[**] of phosphoric acid, such as the mixed anhydrides with aryl sulfonic acids[1], have been used. We wish to introduce a new class of versatile, extremely reactive, phosphorylating agents, namely the five-membered cyclic acyl phosphates *(5)*. Frequently, they permit preparation of phosphoric acid esters in fewer steps than with the common reagents used previously.

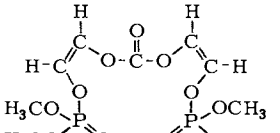


(1), R = H, CH_3, C_6H_5

The reaction of trimethyl phosphite with α-dicarbonyl compounds yields the derivatives of 1,3,2λ⁵-dioxaphosphole *(1)*[2]. *(1)* R = H, undergoes *O*-acylation by phosgene to form *(2)* or *(3)*, respectively[3], depending upon the relative amounts of the reactants, whereas *(1)*, R = CH_3, is *C*-acylated by phosgene (in hexane at 0 °C) to give *(4)* ($\delta^{31}P = +3.0$ ppm, H_3PO_4)[4].

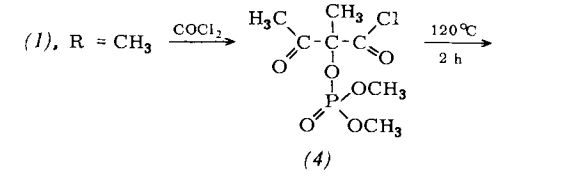


(2)

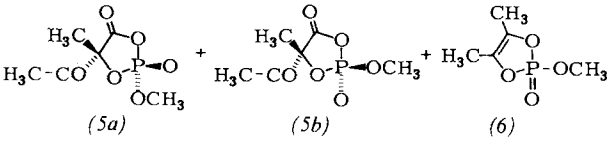


(3)

Upon heating for two hours at 120 °C *(4)* is transformed into a mixture of the diastereomeric cyclic acyl phosphates *(5a)* and *(5b)*, and the known enediol phosphate *(6)*[5] ($\delta^{31}P = -11.6$ ppm, H_3PO_4). The separation of *(5)* and *(6)* can be achieved by short-path distillation *in vacuo*. The prevalent diastereomer *(5b)* ($\delta^{31}P = -2.42$ ppm, H_3PO_4; $\tau = 7.62$, 8.23, and 6.02 ppm; $J_{HP} = 12.0$ Hz, m.p. 82—84 °C) can be obtained in crystalline form, but not the other diastereomer *(5a)* ($\delta^{31}P = -2.66$ ppm (H_3PO_4); $\tau = 7.66$, 8.13, and 6.02 ppm; $J_{HP} = 12.0$ Hz).

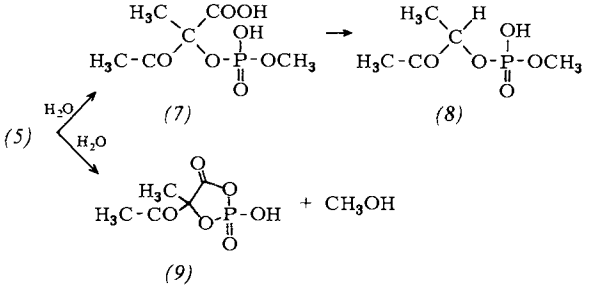


(4)



(5a) *(5b)* *(6)*

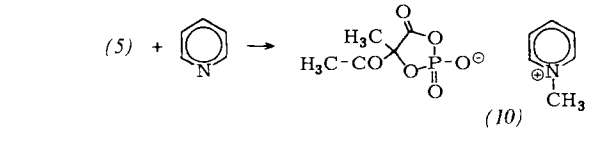
The diastereomers *(5b)* and *(5a)* interconvert in the presence of nucleophiles and form an equilibrium mixture of 70 : 30. At 150 °C *(5)* loses CO_2 to form the enediol phosphate *(6)*. In dioxane or $CDCl_3$ solution[***] *(5)* is hydrolyzed rapidly (in <15 s) by one equivalent of water, mainly *via* the intermediate *(7)*, to the acetoin derivative *(8)*; traces of the cyclic hydrogen phosphate *(9)* and methanol are also produced. The intermediate *(7)* is decarboxylated relatively slowly, and its presence can be demonstrated by esterification with diazomethane.



(7) *(8)* *(5)* *(9)*

With primary and secondary alcohols, *e.g.*, methanol, ethanol, benzyl alcohol, and isopropanol, *(5)* reacts very rapidly, with ring-opening and decarboxylation to yield the acetoin derivatives of type *(12)* [alkyl methyl (1-methyl-2-oxopropyl) phosphates]. In $CDCl_3$[***] the reaction with one equivalent of each of the above alcohols is complete in <15 s, whereas under the same conditions the reaction with *tert*-butanol proceeds with $t_{1/2} \approx 135$ s.

The reactivity of *(5)* toward hydroxyl compounds is higher than that of any previously known organophosphorus compound, including the most reactive, enediol phosphate *(6)*[5] ($t_{1/2} \approx 8$ days for the reaction with one equivalent of *tert*-butanol in $CDCl_3$[***]; $t_{1/2} \approx 150$ s for the reaction with one equivalent of water in dioxane. This pronounced reactivity is due to the fact that *(5)* contains a strongly apicophilic leaving group as part of a five-membered ring[6].



(10)

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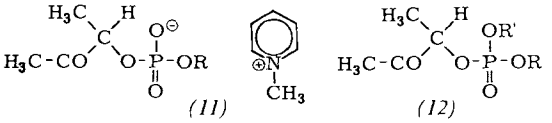
[**] *I.e.*, the P-atom does not belong to a ring.

[***] 0.1 M solution at 24 °C.

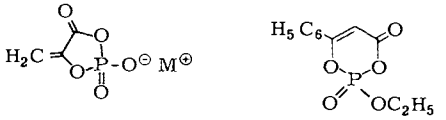
The cyclic acyl phosphate *(5)* *N*-methylates pyridine to yield the salt *(10)*. The structure of *(10)* was demonstrated by the formation of the original cyclic acyl phosphate *(5)* upon treatment with trimethyloxonium tetrafluoroborate. The nucleophilic attack of the pyridine at the methyl carbon of *(5)*—and not at the electrophilic phosphorus atom—can be attributed to the fact that the incipient formation of the C—N bond and the simultaneous rupture of the C—O bond are energetically favored over the initial formation of a P—N bond and cleavage of a P—O bond. This argument is based upon an estimate of activation energies according to *Szabo*'s method[7].



(11) *(12)*

The salt *(10)* undergoes rapid hydrolysis at 25 °C, and yields, after decarboxylation, the compound *(11)*, R = H, while alcoholysis or phenolysis gives *(11)*, R = alkyl or aryl respectively; it reacts substantially faster with primary alcohols than with secondary alcohols.

Since the phosphate esters of α-hydroxy carbonyl compounds are hydrolyzed with particular ease[6], the 3-keto-2-butyloxy groups of the phosphate esters *(11)* and *(12)* can be selectively replaced by hydrogen. Trialkyl phosphates *(12)* are obtained from the compounds *(11)* by known methods. The recyclization of compound *(7)*, and subsequent reaction with an alcohol is an attractive alternative.



(13) *(14)*

To our knowledge, *(5)* is the first isolated example of a five-membered cyclic acyl phosphate. *Clark* and *Kirby*[8] postulated the formation of the five-membered cyclic acyl phosphate *(13)* derived from the enol form of pyruvic acid. *Marecek* and *Griffith*[9] reported the isolation of the six-membered cyclic acyl phosphate *(14)*, derived from benzoyl acetic acid.

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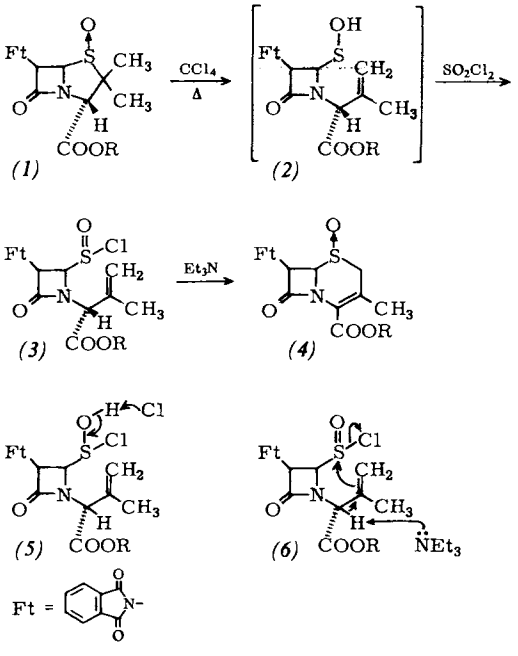
Synthesis of Deacetoxycephalosporin *S*-Oxides by Oxidative Trapping of Sulfenic Acids from Penicillin *S*-Oxides[1]

By *Stjepan Kukolja* and *S. R. Lammert*[*]

Previous studies have shown that sulfenic acids *(2)* can be generated during the heating of penicillin *S*-oxides *(1)*[2]. The high reactivity of sulfenic acids *(2)* has hitherto precluded their isolation, and only intra- and intermolecular trapping of this reactive group has thus far been accomplished. These reactions demonstrated that protonated sulfenic acids exhibit electrophilic properties. However, the sulfur atom in sulfenic acids should also possess some nucleophilic character[3]; to examine this possibility we have studied oxidative trapping of this transient functionality.



(a), R = CH_3; *(b)*, R = *p*-NO_2-$C_6H_4CH_2$

When methyl 7-phthalimidopenicillanate 1-oxide *(1a)* is heated with 1 equiv. of sulfuryl chloride in boiling carbon tetrachloride for 50 min, an inseparable mixture of two isomeric compounds is obtained in a 2 : 1 ratio. The mixture has the composition $C_{17}H_{15}ClN_2O_6$. The IR spectrum exhibits absorptions at 1075 and 1086 cm^{-1}, indicating the presence of a sulfinyl group[4], and it shows the characteristic azetidinone peak at 1800 cm^{-1}. The NMR spectrum of the mixture indicates that the isomers are closely related. The major product gives signals at 117 (s, C—CH_3), 231 (s, CO—OCH_3), 306 (2 vinylic H, and H-3, J = 1.5 Hz), 348 and 356 (d, 2 *cis*-azetidinone H, J = 5.0 Hz), and 470 Hz (4 aromatic H). The minor component shows the following NMR data: 119 (s, 3 H), 228 (s, 3 H), 313 (s, 1 H), 315 (d, 2 H, J = 1.5 Hz), 343 (d, 1 H, J = 5.0 Hz), 356 (d, 1 H, J = 5.0 Hz), and 470 Hz (m, 4 aromatic H).

These data, together with mechanistic considerations, suggest that the mixture consists of two diastereoisomers of the compound methyl 3-methyl-2-(2-chlorosulfinyl-4-oxo-

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3-phthalimido-1-azetidinyl)-3-butenoate *(3a)* which are epimeric at sulfur[5].

The following reaction, which confirms the structural assignment of *(3a)*, is also significant for its synthetic utility: Treatment of *(3a)* with 1 equiv. of triethylamine in dichloromethane or benzene for 5 min at room temperature gives methyl 3-methyl-7-phthalimido-3-cephem-4-carboxylate 1-oxide *(4a)*, m.p. 215 °C, in good yield. The NMR spectrum of *(4a)*, with the characteristic AB pattern of the C-2 methylene protons at 212 and 247 Hz ($J = 16.0$ Hz) and the olefinic methyl singlet at 143 Hz, strongly supports a deacetoxycephalosporin structure. Comparison of *(4a)* with authentic sample prepared by oxidation of methyl 3-methyl-7-phthalimido-3-cephem-1-carboxylate[6] with *m*-chloroperbenzoic acid also substantiates this structure.

The reactions described above with the methyl ester *(1a)* were repeated with the *p*-nitrobenzyl ester *(1b)*. Thus, heating *(1b)* with 1 equiv. of sulfuryl chloride in boiling benzene for 55 min affords *(3b)* in almost quantitative yield. After removing the solvent, the yellow foam is redissolved in benzene, 1 equiv. of triethylamine is added, and the solution is stirred at room temperature for 5 min. The crude product, after a workup procedure, is recrystallized from ethyl acetate and yields *(4b)* as tan crystals, m.p. 198—200 °C, in good yield[7].

We believe that the nucleophilic sulfur in the sulfenic acid grouping is attacked by chlorine (electrophilic and/or a free radical) resulting in the intermediate *(5)*, which after elimination of hydrogen chloride gives *(3)*. Although the absolute configuration at sulfur is not established, the stereochemical course of the reaction is most likely controlled by the bulkiness of the neighboring phthalimido group. Cyclization of *(3)* to *(4)* can be explained by the initial abstraction of the α-proton[8] which increases the nucleophilicity of the double bond. Concomitantly the activated sulfinyl group readily undergoes nucleophilic substitution[9] resulting in formation of the S—C bond and ring closure to the six-membered ring system [see *(6)*].

Other pathways are admittedly also conceivable. Thus, expecting that *(3)* might react with the initiating base to eliminate hydrogen chloride and form the sulfine[10], we monitored the reaction of *(3a)* with triethylamine in chloroform by IR and NMR spectroscopy[11]. However, no evidence could be found for the existence of a sulfine intermediate under the applied conditions[12]. In addition, the sulfine is ruled out as a possible intermediate by the fact that 6-epicephalosporin could not be detected as a reaction product.

To our knowledge the preparation of sulfinyl chlorides by the oxidative trapping of the thermolytically-formed sulfenic acids has no precedent. The simplicity and the high yields make this a convenient preparation of sulfinyl chlorides from tertiary sulfoxides. Cyclization of sulfinyl chlorides to cephem *S*-oxides is a new synthetic method for this class of compounds. A combination of the two reactions provides a useful preparative process for deacetoxycephalosporin *S*-oxides.

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[4] *L. J. Bellamy* in *N. Kharasch*: Organic Sulfur Compounds. Pergamon Press, Oxford 1961, Vol. 1, p. 28; *J. L. Kice* and *K. Ikura*, J. Amer. Chem. Soc. *90*, 7378 (1968).

[5] Tricoordinated sulfur compounds such as sulfonium salts ($R^1R^2R^3S^{\oplus}X^{\ominus}$), sulfoxides ($R^1R^2SO$), sulfinate esters (RSOOR), and sulfinyl halides (RSOHal) are asymmetric and can exist in epimeric forms which are usually stable at room temperature; see *K. Mislow, M. M. Green, P. Laur, J. T. Melillo, T. Simmons*, and *A. L. Ternay, Jr.*, J. Amer. Chem. Soc. *88*, 1958 (1965); *D. C. Garwood* and *D. J. Cram, ibid. 92*, 4575 (1970), and references cited therein.

[6] Prepared from 7-aminodeacetoxycephalosporanic acid and ethyl phthalimidoformate followed by esterification with diazomethane, m.p. 187—188 °C.

[7] Satisfactory elemental analyses were obtained for all new compounds. Compound *(4b)* has been fully characterized by spectroscopic methods.

[8] This abstraction is facile since the α-proton is strongly activated owing to the neighboring ester group and its allylic nature.

[9] *J. L. Kice* and *C. A. Walters*, J. Amer. Chem. Soc. *94*, 590 (1972).

[10] For the preparation of sulfines by elimination of HCl from sulfinyl chlorides see *G. Opitz*, Angew. Chem. *79*, 161 (1967); Angew. Chem. internat. Edit. *6*, 107 (1967), and references cited therein.

[11] The sulfines give two strong IR bands at 1019—1078 and 1065 to 1128 cm^{-1} which are assigned to the C=S=O grouping; see ref. [10], p. 109.

[12] First the NMR spectrum of *(3a)* was measured in $CDCl_3$ and then two drops of triethylamine added, the sample tube was shaken for 5 seconds, and immediately the spectrum between 280 and 380 Hz was recorded. The azetidinone protons of *(3a)* disappeared and were replaced completely by those of *(4a)* in less than 1 minute.

Synthesis of 9,10:15,16-Bis(tetramethylene)cyclooctadeca-7,9,15,17-tetraene-2,4,11,13-tetrayne-1,6-dione, a Tetraalkylated Tetradehydro[18]annulenedione[1][***]

By *Koji Yamamoto* and *Franz Sondheimer*[*]

Whether fully conjugated macrocyclic diketones ("annulenediones") behave as quinones is an interesting question. Such compounds appeared to be unknown, although certain benz-fused[2] and bridged[3] [10]annulenediones have been prepared. We now describe the synthesis of the tetraalkylated tetradehydro[18]annulenedione *(5)*, the first macrocyclic example of this type of diketone.

Oxidative coupling of *(1)*[4] with cupric acetate in pyridine for 2 h at 55 °C led to the "dimer" *(2)* as light yellow crystals from chloroform-ethanol, m.p. 184—185 °C[5], in 55% yield. Reaction of *(2)* with a large excess (*ca.* 25 molar equivalents) of ethynylmagnesium bromide[6] in tetrahydrofuran for 16 h at room temperature gave in 95%

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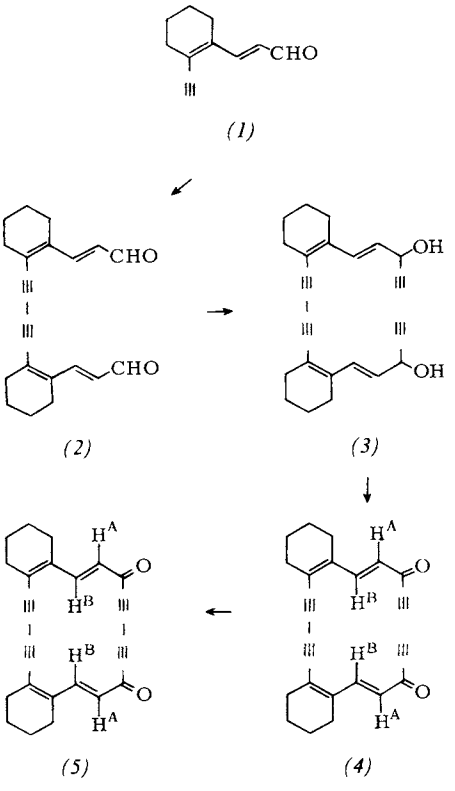
[***] Financial support of this work by the Science Research Council is gratefully acknowledged.

yield the light yellow diol *(3)* (isolated by chromatography on silica gel), presumably as a mixture of *meso* and racemic forms[5]. Oxidation of *(3)* with manganese dioxide[7] in ether for 1 h at room temperature yielded 60% of the diketone *(4)* as yellow prisms from chloroform-pentane, which decomposed on attempted m.p. determination; IR (KBr): 3200 m (C≡CH), 2100 m (C≡C), 1620 s cm^{-1} (C=O); λ_{max} (C_2H_5OH) 236 (ε 22900), 273 (14800), 332 (20200), 372 (19800), 383 (20000), 420 sh nm (14600); NMR (60 MHz, $CDCl_3$): τ 1.78 (2H/d, J = 17 Hz, H^B), 3.69 (2H/d, J = 17 Hz, H^A), 6.58 (2H/s, acetylenic H), 7.4—7.9 (8H/m, allylic CH_2), 8.0—8.5 (8H/m, nonallylic CH_2).



The diketone *(4)* could not be oxidatively coupled with cupric acetate in pyridine, since it is decomposed by pyridine. However, this reaction was carried out successfully by means of oxygen, cuprous chloride, and ammonium chloride in aqueous ethanol and benzene (2 h at 65 °C). Chromatography on silica gel and crystallization from chloroform-pentane then gave the cyclic diketone *(5)* in 25% yield [as well as 50% of recovered *(4)*] as relatively stable bright red needles, which decomposed on attempted m.p. determination.

The fact that *(5)* is the cyclic "monomer" was shown by the mass spectrum (strong molecular ion peak at *m/e* 364). The IR spectrum [2140 m (C≡C), 1625 s cm^{-1} (C=O)] was similar to that of *(4)*, except for the absence of the 3200 cm^{-1} (C≡CH) band. In the electronic spectrum of *(5)* [λ_{max} (C_2H_5OH) 275 (ε 9500), 293 (16900), 312 (29000), 333 (29400), 460 nm (2900), with absorption >550 nm], the most intense maxima were shifted hypochromically compared with those of *(4)*, but the highest wavelength band was shifted bathochromically.

The NMR spectrum of *(5)* (60 MHz, $CDCl_3$) showed resonances at τ 0.94 (2H/d, J = 17 Hz, H^B), 3.82 (2H/d, J = 17 Hz, H^A), 7.4—7.9 (8H/m, allylic CH_2), and 8.1—8.5 (8H/m, nonallylic CH_2). The main difference in the NMR spectra of *(4)* and *(5)* [except for the acetylenic proton band in *(4)*] is the downfield shift of *ca.* 0.8 ppm of the "inner" H^B proton resonance in *(5)* as compared to *(4)*. This is presumably due to the fact that H^B in the relatively rigid structure *(5)* is deshielded by the surrounding ethylenic and/or acetylenic bonds to a greater extent than in *(4)*, where free rotation about the single bonds can take place[8].

Experiments are now in progress to obtain information regarding the possible quinonoid nature of *(5)*.

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[1] Unsaturated Macrocyclic Compounds. Part 99. — Part 98: *K. Grohmann, P. D. Howes, R. H. Mitchell, A. Monahan,* and *F. Sondheimer,* J. Org. Chem., in press.

[2] *J. Suszko* and *R. Schillak,* Roczniki Chem. *14*, 1216 (1934); *K. Suzuki,* Bull. Chem. Soc. Jap. *35*, 735 (1962).

[3] *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); *E. Vogel, W. A. Böll,* and *E. Lohmar,* Angew. Chem. *83*, 403 (1971); Angew. Chem. internat. Edit. *10*, 399 (1971).

[4] *R. H. McGirk* and *F. Sondheimer,* Angew. Chem. *84*, 897 (1972); Angew. Chem. internat. Edit. *11*, 834 (1972).

[5] The assigned structure was confirmed by the IR, UV, and ^{1}H-NMR spectra.

[6] *E. R. H. Jones, L. Skatteböl,* and *M. C. Whiting,* J. Chem. Soc. *1956*, 4765; Org. Synth. *39*, 56 (1959).

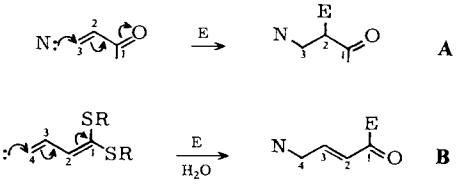
[7] *J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen,* and *T. Walker,* J. Chem. Soc. *1952*, 1094.

[8] *P. J. Beeby* and *F. Sondheimer,* J. Amer. Chem. Soc. *94*, 2128 (1972).

"Michael-type" Addition to Conjugated Ketene Thioacetals[**]

By *Dieter Seebach, Michael Kolb,* and *Bengt-Thomas Gröbel*[*]

By Michael addition we understand the synthetically most valuable, nucleophilic attack on C-3 of the chain of an α,β-unsaturated carbonyl compound (process **A**, where the



electrophile E is usually a proton). We here describe the first examples of the complementary process **B**, in which a nucleophile adds to C-4 of a carbonyl derivative.

The dienes *(1)*, *(3)*, *(7)*, and *(9)* can be prepared in high yields from 2-lithio-2-(trimethylsilyl)-1,3-dithiane[11] and α,β-unsaturated aldehydes (acrolein or crotonaldehyde) or ketones (methyl vinyl ketone or cyclohexenone[11]) and react with alkyllithiums in the above-mentioned sense in THF at −80 to −20 °C. In this way, by successive addition of *n*-butyllithium and methyl iodide we obtained the thioacetals of α,β-unsaturated methyl ketones *(2)*, *(4)*,

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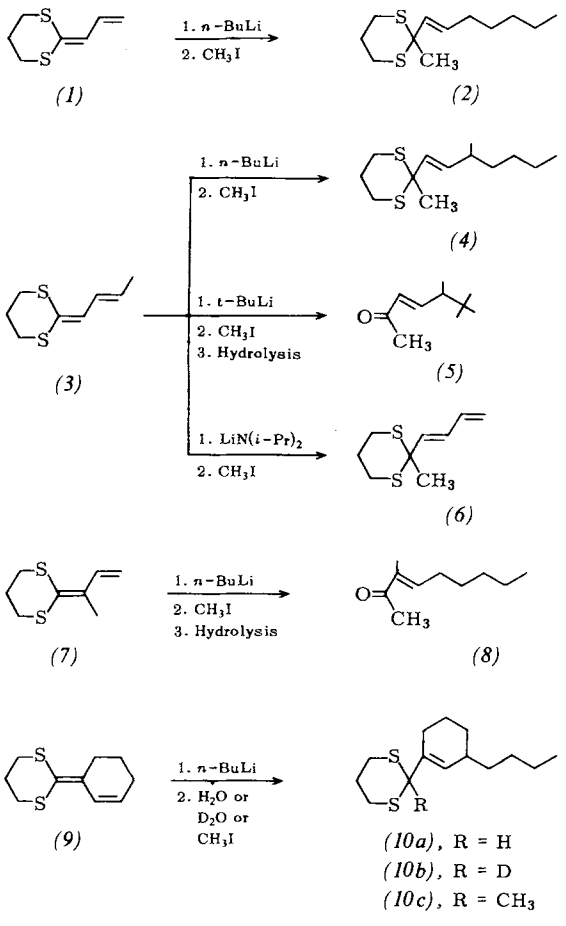
and *(10c)* in almost quantitative yields; protonolysis or deuterolysis of the primary adducts led similarly to the aldehyde derivatives *(10a)* and *(10b)*, respectively.



Neutral hydrolysis of the thioacetals by mercuric chloride and oxide in methanol afforded the free carbonyl compounds, *e.g. (5)* from *(3)*, *tert*-butyllithium, and methyl iodide, also *(8)* from *(7)*, *n*-buthyllithium, and methyl iodide.

Obviously, nucleophilic addition of butyllithium occurs even if, as in *(3)*, *(7)*, and *(9)*, the diene contains allylic hydrogen atoms that are removable as protons. That these atoms can be removed by a suitable base (lithium diisopropylamide) is shown by conversion of *(3)* into *(6)* which is a masked acylbutadiene of interest for Diels-Alder reactions.

The new compounds gave correct elemental analyses; according to NMR analysis (see Table 1; 16Hz-*trans*-coupling), the double bonds in the products have the *trans*-configuration shown in the formulas.

The results described are a valuable extension of the synthetic utility of metalated thioacetals: for instance, orienting experiments show that other alkyllithium compounds behave like butyllithium; the ketene thioacetals used are accessible by a reaction of large scope, and of course[2] the methyl iodide may be replaced by many other electrophiles.

[1] *D. Seebach et al.*, Angew. Chem. *84*, 476 (1972); Angew. Chem. internat. Edit. *11*, 443 (1972). The same reaction has been published almost simultaneously by two other schools: *F. Jones* and *M. F. Lappert*, J. C. S. Chem. Comm. *1972*, 526; *A. Carey* and *A. S. Court*, J. Org. Chem. *37*, 1926 (1972).

[2] *D. Seebach*, Synthesis *1969*, 17; Angew. Chem. *81*, 690 (1969); Angew. Chem. internat. Edit. *8*, 639 (1969).

Table 1. ^{1}H-NMR data of compounds *(2)*—*(9)* and *(10c)* [a].

Compound	δ [ppm] Methyl-H [b]	Vinyl-H
(2)	s, 1.62	1 H/d, 5.55 1 H/m, 5.90
(3)	d, 1.77	1 H/m, 5.69 2 H/m, 6.45
(4)	dithiane-CH_3: s, 1.55 CH_3: d, 1.05	2 H/m, 5.35–5.85
(5) [c]	keto-CH_3: s, 2.22 CH_3: d, 1.03 *t*-Bu: s, 0.92	1 H/d, 6.10 1 H/m, 6.80 2 H/m, 5.15
(6)	dithiane-CH_3: s, 1.61	1 H/m, 5.75 2 H/m, 6.35
(7)	s, 1.90	2 H/m, 5.10 1 H/m, 7.20
(8) [d]	CH_3: s, 1.78 keto-CH_3: s, 2.28	1 H/m, 6.62
(9)		1 H/m, 5.80 1 H/m, 6.70
(10c) [e]	dithiane-CH_3: s, 1.52	1 H/m, 6.15

[a] *(1)* was not isolated.
[b] Without the terminal CH_3 group of the alkyl chain.
[c] M.p. of the 2,4-dinitrophenylhydrazone, 134.5—135.0°C; IR, 1675 cm^{-1}.
[d] IR, 1670 cm^{-1}.
[e] *(10a)*: dithiane-H s 4.40 ppm, which is not shown by *(10b)*.

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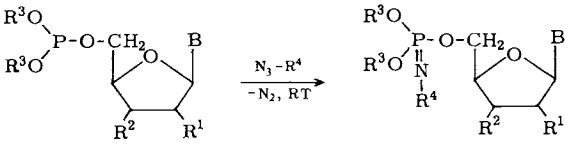
Imidophosphates as New Nucleotide Derivatives

By *Gerhard Baschang* and *Vratislav Kvita*[*]

Although phosphoric diester amides are obtained from trialkyl or triaryl phosphites and aliphatic azides[1,2], the analogous reaction with sulfonyl, phosphoryl or acyl azides gives trialkyl or triaryl imidophosphates[3]. We have prepared compounds *(2)* of this type from 5′-phosphorous esters *(1)* of uridine, cytidine, and thymidine[4] and the azides R^4N_3 (see Table 1).



(1) *(2)*

This reaction proceeds quantitatively when an excess of azide is used at room temperature. We prepared the nucleoside 5′-phosphite esters *(1)* from the corresponding protected nucleoside derivatives and chlorophosphites in the presence of 2,6-lutidine; they were not isolated but were used directly for further work. 5′-Imidophosphates of adenosine are unstable; they decompose with loss of the

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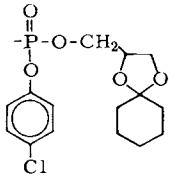
Table 1. Properties of the compounds *(2)* prepared [a]. U = uracil, N^4—Ac—C = N^4-acetylcytosine, T = thymine.

B	R^1	R^2	R^3	R^3	R^4	λ_{max} [nm] (CH_3OH)	$\varepsilon \cdot 10^{-3}$ [b]	$[\alpha]_D^{20}$ [°]	Yield [%][c]	Chromatogr. eluent
U[f]	—O—$C(CH_3)_2$—O—		—CH_2—$C(CH_3)_2$—CH_2—		SO_2CH_3	256	10.58	+14.2 ($CHCl_3$)	50	ethyl acetate: acetone 9:1
U[d]	—O—$C(CH_3)_2$—O—		—CH_2—$C(CH_3)_2$—CH_2—		$P(O)(OC_6H_5)_2$	257	10.18	+ 3.7 ($CHCl_3$)	97	$CHCl_3$:CH_3OH 95:5
U	—O—$C(CH_3)_2$—O—		—CH_2—$C(CH_3)_2$—CH_2—		[e]	217 256	15.4 12.12	+12.7 (CH_3OH)	70	$CHCl_3$:acetone 6:4
N^4—Ac—C [f]	$OCOCH_3$	$OCOCH_3$	—CH_2—$C(CH_3)_2$—CH_2—		[e]	213 247 295	22.75 16.20 6.55	+25 (CH_3OH)	65	$CHCl_3$:acetone 6:4
T	H	—$OP(OC_2H_5)_2$ ‖ NSO_2CH_3	C_2H_5	C_2H_5	SO_2CH_3	264	10.63	+ 2 ($CHCl_3$)	56	benzene:C_2H_5OH 8:2

[a] All the compounds gave correct elemental analyses and were characterized by NMR spectra (100 MHz).
[b] The UV spectra were measured on a Beckman DBG instrument.
[c] Total yield (not optimized) of the reactions: nucleoside derivate → *(1)* → analytically pure *(2)*.
[d] M.p. 122 °C.
[e]



[f] Not stable towards rat liver homogenate (see following communication); the other compounds were stable.

phosphate group to give a salt of the adenosine cyclonucleoside.

General procedure:

2-Chloro-5,5-dimethyl-1,3,2-dioxophosphorinane or another chlorophosphite (1.5–2 equivalents) is added dropwise with cooling (10–20 °C) to a mixture of a 10% solution of the protected nucleoside in dioxane and 2 equivalents of 2,6-lutidine. After 15 h at room temperature the mixture is treated with the azide (3 equivalents; see Table 1) and set aside for a further 15 h until nitrogen evolution is complete. The precipitated lutidinium chloride is then removed, the filtrate is evaporated in a vacuum and the residue is chromatographed on silica gel 60 (Merck) with the solvent listed in Table 1.

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[1] *W. Freist, K. Schattka, F. Cramer,* and *B. Jastorff*, Chem. Ber. *105*, 991 (1972).
[2] *V. Kvita* and *G. Baschang*, Helv. Chim. Acta *55*, 2683 (1972).
[3] *M. I. Kabachnik* and *V. A. Gilyarov*, Izv. Akad. Nauk SSSR, Otdel. Khim. Nauk *1956*, 790; *1961*, 819; Chem. Abstr. *51*, 1823b (1957).
[4] See *G. Baschang* and *V. Kvita*, Angew. Chem. *85*, 44 (1973); Angew. Chem. internat. Edit. *12*, 71 (1973).

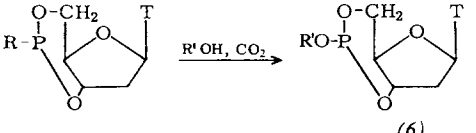
New Derivatives of Thymidine 3′,5′-Cyclophosphate

By *Gerhard Baschang* and *Vratislav Kvita*[*]

Extension of the reaction of sulfonyl, phosphoryl, and acyl azides with trialkyl phosphites to nucleoside phosphorous esters opened a simple and mild route to new nucleotide derivatives[1] that interested us because of their presumed stability towards phosphatases. We expected the same properties from the thymidine 3′,5′-cyclophosphate derivatives *(2)*—*(5)* that we prepared from thymidine by way of its 3′,5′-cyclophosphite *(1a)*.

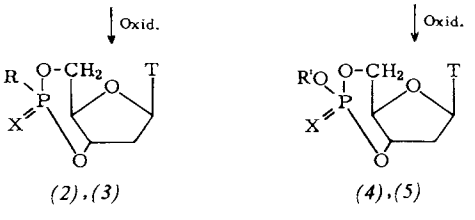
Thymidine was treated with $RP[N(CH_3)_2]_2$ in dioxane at 80 °C or in dioxane in the presence of CO_2 at 20—50 °C, yielding compounds of type *(1)*. If alkoxybis(dimethylamino)phosphanes are used in place of tris(dimethylamino)-phosphane, the yield of cyclophosphite *(1)* is increased from 20% to about 40% (determined spectrophotometrically). The cyclophosphites were not isolated because of their sensitivity to hydrolysis, but were brought at once into further reaction.

On oxidation with $KMnO_4$, hydroperoxides or peroxy acids (sometimes after replacement of the dimethylamino group by an alkoxy or aryloxy group), *(1a)* afforded the thymidine 3′,5′-cyclophosphates *(3)*—*(5)* or on oxidation by methylsulfonyl azide the corresponding imidophosphate *(2)* (see Table 1). Replacement of the dimethylamino group of *(1a)* by alkoxy groups on reaction with alcohols and CO_2 yielding compounds of type *(6)* by way of a carbamoyl phosphite is known[2] and occurs, as we found, also very readily with phenols.



(1a), R = $N(CH_3)_2$
(1b), R = $O\text{-}nC_4H_9$
(1c), R = OCH_3

(6)



(2), *(3)* *(4)*, *(5)*

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Table 1. Properties of the compounds *(2)*—*(5)* prepared from *(1a)*. T = thymine [a].

Cpd.	X	R or R'	λ_{max} [nm] (CH_3OH)	$\varepsilon \cdot 10^{-3}$ [b]	M.p. [°C] [c]	$[\alpha]_D^{20}$ ($CHCl_3$) [°]	Yield [%] [d]	Chromatogr. eluent [e]
(2)	CH_3SO_2N	$N(CH_3)_2$	262	10.5	210	−24.4	20	acetone:$CHCl_3$ 8:2
(3)	O	$N(CH_3)_2$	264	9.78	230	−41.1	20	ethyl acetate:C_2H_5OH 8:2
(4)	O	*p*-AcO—C_6H_4	262	10.4	137	−43.9	18	$CHCl_3$:C_2H_5OH 14:1
(5)	O	*p*-C_6H_5—C_6H_4	252	29.1	220	−8.6	17	$CHCl_3$:C_2H_5OH 14:1

[a] All the compounds gave correct elemental analyses and were characterized by NMR spectra (100 MHz).
[b] The UV spectra were measured with a Beckman DBG instrument.
[c] Not corrected.
[d] Total yield thymidine → *(1a)* → *(6)* → product.
[e] Preparative chromatography on silica gel 60 (Merck).

To our knowledge it was not possible to obtain nucleoside 3',5'-cyclophosphoric esters by the methods previously recorded.

The stability toward phosphatases: Compounds *(2)*—*(5)* were incubated with rat liver homogenate and tris buffer pH = 7.2 at 37 °C. *(4)* is sensitive to hydrolysis and was cleaved; *(2)*, *(3)*, and *(5)* were stable.

Thymidine 3',5'-cyclo(dimethylamino)phosphite (1a)

Tris(dimethylamino)phosphane (0.5 ml) is added to a suspension of thymidine (1.2 g) in anhydrous dioxane (50 ml), and the mixture is heated slowly with stirring to 80 °C and kept for 8 h at that temperature. The resulting solution can be treated directly with methanesulfonyl azide to afford *(2)*. For oxidation to *(3)* and *(4)* the dioxane solution is evaporated in a vacuum and *(1a)* is extracted at room temperature by ethyl acetate.

Thymidine 3',5'-cyclo(dimethylamino)-N-(mesylimido)-phosphate (2)

Methanesulfonyl azide (2 equivalents) is added to a dioxane solution of *(1a)* which is then set aside at room temperature for 15 h and finally evaporated to dryness in a vacuum. The residue is chromatographed (see Table 1); *(2)* is eluted first.

Thymidine 3',5'-cyclo(dimethylamino)phosphate (3)

m-Chloroperoxybenzoic acid (1.1 equivalents), followed after 10 min by 2,6-lutidine (1.1 equivalents), is added to an ethyl acetate solution of *(1a)*, which is then evaporated in a vacuum. The residue is chromatographed (see Table 1), *(3)* being eluted first.

Thymidine 3',5'-cyclo(p-acetoxyphenyl)phosphate (4)

p-Acetoxyphenol (3 equivalents) is added to an ethyl acetate solution of *(1a)*, into which CO_2 is then led at room temperature for about 40 h. Next *tert*-butyl hydroperoxide (1.1 equivalents) is added and the mixture is evaporated in a vacuum. The residue is chromatographed, the excess of *p*-acetoxyphenol being eluted before the *(4)*.

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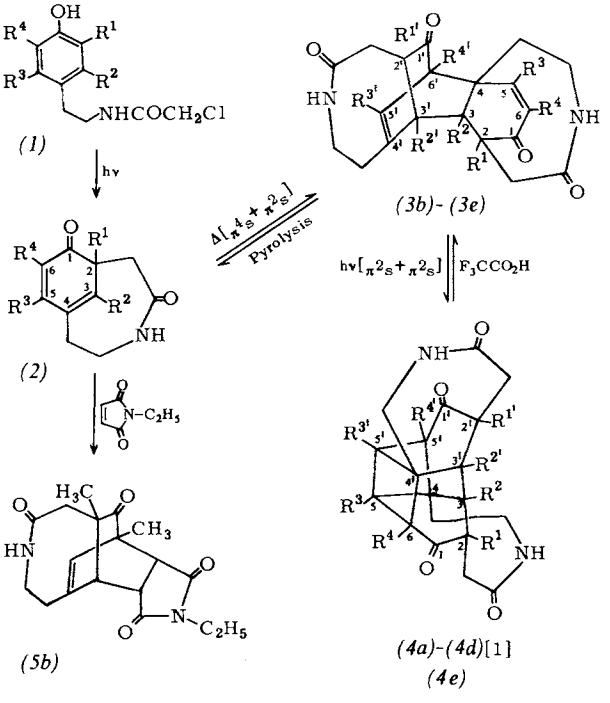
[1] *G. Baschang* and *V. Kvita*, Angew. Chem. *85*, 43 (1973); Angew. Chem. internat. Edit. *12*, 70 (1973).

[2] *N. K. Kochetkov, E. E. Nifant'ev, I. P. Gudkova*, and *M. P. Koroteev*, Zh. Obshch. Khim. *40*, 2199 (1970).

Transient Cyclohexadienones by Novel Reversal Reactions from Cage Photodimers Derived from *N*-Chloroacetyltyramines

By *Takeo Iwakuma, Osamu Yonemitsu, Nobuaki Kanamaru, Katsumi Kimura*, and *Bernhard Witkop*[*]

Recently we reported that on irradiation *N*-chloroacetyltyramine derivatives *(1)* give novel cage compounds



(1a), R^1,R^2,R^3,R^4 = H
(1b), R^1,R^4 = CH_3, R^2,R^3 = H
(1c), R^1,R^3 = CH_3, R^2,R^4 = H
(1d), R^2,R^3 = CH_3, R^1,R^4 = H
(1e), R^1,R^2 = CH_3, R^3,R^4 = H

(2a)—*(2d)* see text
(2e)-A, R^1,R^2 = CH_3, R^3,R^4 = H
(2e)-B, R^3,R^4 = CH_3, R^1,R^2 = H
(3e), $R^{1'},R^{2'},R^3,R^4$ = CH_3, $R^1,R^2,R^{3'},R^{4'}$ = H

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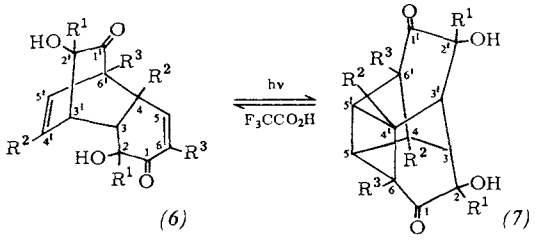
(4), probably *via* intermediate 2,4-cyclohexadienones *(2)* and subsequent $[_{\pi}4_s + _{\pi}2_s]$ and $[_{\pi}2_s + _{\pi}2_s]$ cycloadditions[1].

Although cyclohexadienones easily rearrange photochemically[2] and undergo ring opening by the addition of solvents[3], we failed to detect *(2)* as an intermediate by these reactions. However, the first direct evidence for the intermediacy of 2,4-cyclohexadienones *(2)* was provided by flash photolysis in the presence of dienophiles.

When a solution (0.4 mM) of *N*-chloroacetyltyramine *(1a)* in ethanol-water (1:9) was flash-photolyzed at room temperature[4], a transient absorption at $\lambda_{max} = 325$ nm was observed, which must be due to the 2,4-cyclohexadienone *(2a)*[4]. The decay curve followed second-order kinetics ($k = 5.3 \times 10^3$ l mol^{-1} s^{-1}). The relatively large rate constant indicates rapid thermal dimerization under steady-state irradiation without photolysis of the cyclohexadienone. Compounds *(1b)* and *(1c)* gave similar results [*(2b)*: $\lambda_{max} = 333$ nm, $k = 2.0 \times 10^3$ l mol^{-1} s^{-1}. *(2c)*: $\lambda_{max} = 339$ nm, $k = 1.1 \times 10^3$ l mol^{-1} s^{-1}].



(6) *(7)*

(6a), $R^1, R^3 = CH_3$, $R^2 = H$ [7]
(6b), $R^1, R^2, R^3 = CH_3$ [7]
(6c), $R^1 = CH_2Cl$, $R^2, R^3 = H$, m.p. 175—176 °C (dec.)
(6d), $R^1, R = CH_3$, $R^3 = H$

(7a), [1]
(7b), m.p. 246—248 °C (73%)
(7c), m.p. 228—229 °C (38%)
(7d), m.p. 226—227 °C (82%)

The second proof was chemical: When *(1b)* was irradiated with a 10-W low pressure lamp in the presence of 2 equivalents of *N*-ethylmaleimide a Diels-Alder adduct *(5b)* was isolated in 29% yield accompanied by *(4b)* (17%). The structure of *(5b)* (m.p. 161—163 °C) was easily confirmed by mass and NMR spectra.

The photolysis of *(1d)* gave unidentified products with a trace of *(4d)*, detectable by mass spectrometry [410 (M^+)]. The steric hindrance of the methyl group on C-3[5] makes *(2d)* a less reactive dienophile and renders formation of the dimer *(4d)* commensurately more difficult, though *(2d)* is detectable by flash photolysis ($\lambda_{max} = 340$ nm). Interestingly, the 2,3-dimethyltyramine *(1e)* formed two dienones *(2e)-A* and *(2e)-B*, which acted both as diene and dienophile, respectively, to give the dimer *(4e)* (m.p. 296—298 °C, dec.) in 35% yield.

The presence of *(3)* is suggested by analogy with the same type of cage compound obtainable by irradiation of a simple dienone dimer[1,6]. In addition we have now obtained *(3)* from *(4)* by a novel acid-catalyzed reversion reaction. When *(4b)* was digested with trifluoroacetic acid for 1 h at room temperature, *(3b)* (m.p. 292—295 °C) was isolated in 80% yield [^{1}H-NMR (D_6-DMSO, 120 °C[7]): $\delta = 5.14$ (1 H/s, —C=CH—), 5.94 (1 H/s, —CO—C=CH—); mass: 410 (M^+); UV (CH_3OH): $\lambda_{max} = 250$ nm ($\varepsilon = 5100$)].

Under similar conditions *(4e)* also gave *(3e)* (m.p. 315—317 °C, dec.) in 85% yield, whereas *(4a)* and *(4c)* remained unchanged after standing overnight in trifluoroacetic acid. However, on refluxing for 22 h, *(4c)* gave *(3c)* (m.p. > 320 °C) in 70% yield.

Among the model cage compounds *(7a)*, *(7b)*[6], *(7c)*, and *(7d)*[6] readily obtained photochemically from the corresponding dienone dimers[8,9], *(7b)* reverted to *(6b)* quantitatively within 5 min[10], and *(7d)* to *(6d)* in 80% yield after 30 min in CF_3CO_2H. Yet *(7a)* and *(7c)* gave no trace of *(6a)* and *(6c)*, even after refluxing for 17 h. It would appear that the stabilization of a carbonium cation at C-4' determines the ease of cleavage in this acid-catalyzed reversion reaction. In addition, a substituent at C-6 in *(7)* accelerates the reaction, probably because of steric repulsion between alkyl substituents at C-4' and C-6. A detailed kinetic analysis is now in progress.

Irradiation of the enones *(3b)*, *(3c)*, and *(3e)* regenerated the photodimers *(4b)*, *(4c)*, and *(4e)* in yields of 87, 84, and 77%, respectively. Finally, pyrolysis of *(3b)* in the presence of a ten-fold excess of *N*-ethylmaleimide gave *(5b)* in 13% yield, thus affording additional evidence for the intermediacy of the 2,4-cyclohexadienone *(2b)*.

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N-Sulfenylamino Acid *N*-Carboxyanhydrides

By *Hans R. Kricheldorf*[*]

Although the attempted acylation of amino acid *N*-carboxyanhydrides (NCA's) with carbonyl, sulfonyl and phosphoryl chlorides fails and silylation leads to rearrangement of the anhydride ring[1-3], α- and β-amino acid NCA's can be rapidly and quantitatively acylated by reactive sulfenyl chlorides. In this connection particular interest attaches to *o*-nitrophenylsulfenyl (NPS) derivatives because the *o*-nitrophenylthio group can be removed under mild conditions[4-6].

Unlike the unsubstituted NCA's, the NPS-NCA's *(1)* to *(5)* (Table 1) cannot be polymerized and thus are appreci-

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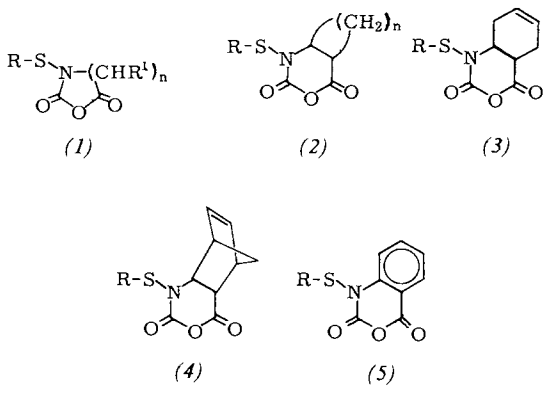


(1) (2) (3)

(4) (5)

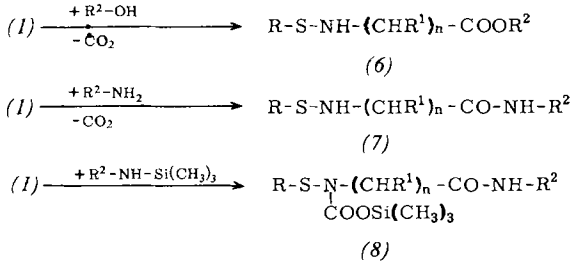
R = o-NO_2-C_6H_4, n = 1,2

Table 1. Properties of the *N*-sulfenylamino acid *N*-carboxyanhydrides *(1)*—*(5)* [a], R = *o*-nitrophenyl.

Cpd.	n	R^1	Yield [%]	M.p.[°C]
(1a)	1	H	92	168–170
(1b) (D, L)	1	$CH(CH_3)_2$	88	125–127
(1c) (L)	1	CH_2—C_6H_5	93	151–153
(1d)	2	H	72	130–132
(2a)	1		85	142–145
(2b)	2		95	126–128
(3)			92	188–191
(4)			94	142–144
(5)			86	231–233

ably more stable on storage, but they decarboxylate more or less rapidly when melted. The electrophilic reactivity of the carbonyl group is similar to that of the parent unsubstituted NCA's. For example, NPS-amino esters *(6)* are obtained by reaction with alcohols, NPS-amino amides *(7)* from amines, and (silyloxycarbonyl) NPS-amino amides *(8)* from *N*-silylated amines. NPS-NCA's are useful for peptide synthesis because their preparation is free from racemization, their reactivity is suitable, and these activated amino acid derivatives crystallize well.

The IR spectra of all the NPS-NCA's in KBr show a usually short, broad band at 2.8—2.9 μm (3440—3540 cm^{-1}) and two carbonyl bands, these being at 5.40 μm (1850 cm^{-1}) and 5.60 μm (1785 cm^{-1}) for *(1)*, n = 1, at 5.48 μm (1825 cm^{-1}) and 5.70 μm (1755 cm^{-1}) for *(1)*, n = 2, at 5.55 μm (1800 cm^{-1}) and 5.70 μm (1755 cm^{-1}) for *(2)*—*(4)*, and at 5.63 μm (1780 cm^{-1}) and 5.75 μm (1740 cm^{-1}) for *(5)*.



(1) $\xrightarrow[-CO_2]{+R^2\text{-}OH}$ R-S-NH-$(CHR^1)_n$-$COOR^2$ *(6)*

(1) $\xrightarrow[-CO_2]{+R^2\text{-}NH_2}$ R-S-NH-$(CHR^1)_n$-CO-NH-R^2 *(7)*

(1) $\xrightarrow{+R^2\text{-}NH\text{-}Si(CH_3)_3}$ R-S-N-$(CHR^1)_n$-CO-NH-R^2, $COOSi(CH_3)_3$ *(8)*

NPS-L-Phenylalanine-NCA (1c)

L-Phenylalanine-NCA (0.1 mol) and *o*-nitrophenylsulfenyl chloride (0.1 mol) are dissolved in anhydrous ethyl acetate (300 ml) or THF, and triethylamine or 4-methylmorpholine (0.1 mol) is added dropwise with ice-cooling. After 30 min the solution is filtered and most of the solvent evaporated in a vacuum. Addition of carbon tetrachloride/light petroleum with ice-cooling affords crystalline *(1c)* (32 g, 93%).

NPS-D,L-Valine amide

A solution of NPS-valine-NCA *(1b)* (0.025 mol) in anhydrous ethyl acetate (100 ml) is stirred with a solution of NH_3 (*ca.* 0.03 mol) in THF (50 ml) for 5 min at 25 °C and the mixture is thereafter heated for 5 min at the boiling point. The solution is then shaken with 5% citric acid solution; the organic phase is separated, dried and evaporated, yielding a crystalline product (6.2 g, 92%) of m. p. 166 to 168 °C.

NPS-L-Phenylalanylglycine

A solution of NPS-L-phenylalanine-NCA *(1c)* (0.025 mol) in anhydrous ethyl acetate is mixed with one of *N*-(trimethylsilyl)glycine trimethylsilyl ester (0.025 mol) in anhydrous dioxane (80 ml) and the whole is boiled for 2 min. The mixture is then shaken with a concentrated ammonium sulfate solution (causing evolution of CO_2). On evaporation and cooling of the dried organic phase a crystalline product (8.8 g, 94%) separates having m. p. 185—187 °C and $[\alpha]_D^{20} = 30.5° \pm 0.5°$ (m.p. 188—190 °C, $[\alpha]_D^{20} = 32°$[4]).

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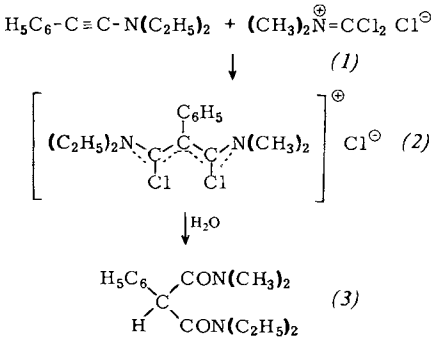
"Biuret Trichlorides" from *N*-Dichloromethylene-*N*,*N*-dimethylammonium Chloride and Dimethylcyanamide[1]

By *Zdenek Janousek* and *Heinz Günter Viehe*[*]

Electron-rich multiple bonds such as in enamines[2] and ynamines[3] very readily undergo addition reactions with *N*-dichloromethylene-*N*,*N*-dimethylammonium chloride ("phosgeneimmonium chloride") *(1)*. Thus diethylaminophenylacetylene and *(1)* form 1,3-dichlorotrimethinecyanine *(2)*[4], which on hydrolysis produces the phenyl malonic diamide derivative *(3)*.



H_5C_6-C≡C-N$(C_2H_5)_2$ + $(CH_3)_2\overset{\oplus}{N}$=$CCl_2$ $Cl^{\ominus}$ *(1)*

$(C_2H_5)_2N$, C_6H_5, $N(CH_3)_2$, Cl, Cl $Cl^{\ominus}$ *(2)*

H_2O

H_5C_6, $CON(CH_3)_2$, H, $CON(C_2H_5)_2$ *(3)*

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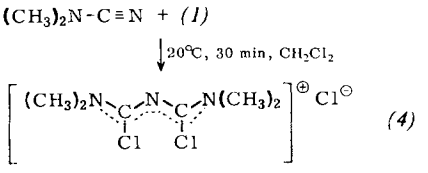
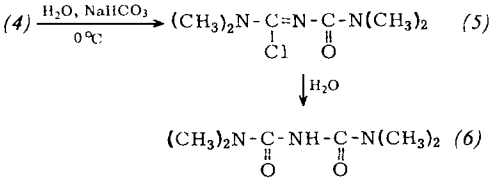
Dialkylcyanamides are electron-rich nitriles and react with *(1)* analogously to ynamines. A smooth addition occurs even at room temperature in methylene chloride solution to give almost quantitative yields of the new 1,3-dichloro-2-azatrimethinecyanines *(4)*, which may be considered as "biuret trichlorides"

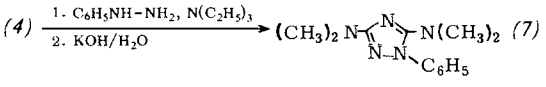


(4)

The hydrolysis of *(4)* leads under mild conditions to N^1,N^1-dimethyl-N^2-(dimethylcarbamoyl)chloroformamidine *(5)* and subsequently to the expected biuret derivative *(6)*.



Like *(2)*, the new azacyanine *(4)* is a versatile bis-electrophilic reagent, particularly for the synthesis of heterocycles. Thus reaction of *(4)* with phenylhydrazine gives the new 1,2,4-triazole derivative *(7)* in 93% yield.



N,N,N',N'-tetramethyl-1,3-dichloro-2-azatrimethinecyanine (4):

Dimethylcyanamide (1.29 g, 18.5 mmol) is added at 20 °C to a stirred suspension of *(1)* (3.0 g, 18.5 mmol) in dry methylene chloride (15 ml). The majority of the solvent is distilled off and the residue treated with about 20 ml of dry ether, whereupon 3.29 g (93%) of *(4)* precipitates as colorless crystals (m.p. 157—161 °C (dec.)) which are stable in a dry atmosphere. NMR ($CDCl_3$): $\delta = 3.59$ and 3.64 ppm; UV (CH_2Cl_2): $\lambda_{max} = 282$ nm ($\varepsilon = 32000$).

N^1,N^1-Dimethyl-N^2-(dimethylcarbamoyl)chloroformamidine (5):

Azacyanine *(4)* (2.32 g, 10 mmol) dissolved in CH_2Cl_2 (20 ml) is hydrolyzed with H_2O (4 ml) and an excess of $NaHCO_3$ for 2 h at 0 °C. The organic phase is dried over $MgSO_4$ and fractionated to give 1.26 g (71%) of *(5)* as a colorless oil (b.p. 120 °C/0.7 torr), which is soluble in water. NMR (CCl_4): $\delta = 2.86$ and 3.14 ppm (two s); IR (film): $\nu = 2925$, 1640, 1485, 1438, 1457, 1260, and 1170 cm^{-1}; mass spectrum: 177 (M^+), 133, 105, 72.

3,5-Bis(dimethylamino)-1-phenyl-1,2,4-triazole (7):

A mixture of phenylhydrazine (1.08 g, 10 mmol) and triethylamine (3.4 g) is added to a stirred solution of *(4)* (1.97 g, 8.5 mmol) in dry methylene chloride (40 ml) over a period of two hours at room temperature. After refluxing for a further hour, the mixture is cooled to −10 °C and treated with concentrated aqueous potassium hydroxide (10 ml). The organic phase is separated, dried over K_2CO_3 and the crude *(7)* distilled. *(7)* (b.p. 122 °C/0.3 torr; yield 1.83 g (93.4%)), is a colorless oil which solidifies at ambient temperature (m.p. 75—77 °C (from water)). NMR ($CDCl_3$): $\delta = 2.75$, 2.96 (12H/2 s), 7.20—7.70 ppm (5H/br); IR (film): $\nu = 1580$, 1545, 1500, 1410, 1376 cm^{-1}; mass spectrum: 231 (M^+).

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Mechanism of Cleavage of Diethyl Ether by Alkyllithium Compounds: Differing Mechanisms of Decomposition of α- and β-Deuterated Diethyl Ether[**]

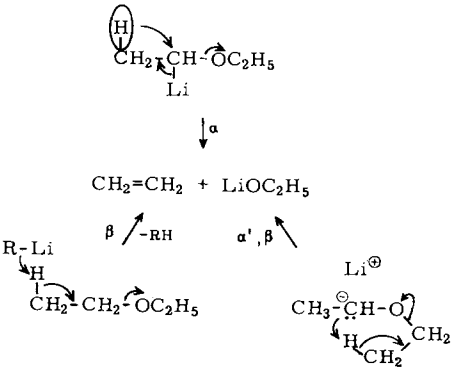
By *Adalbert Maercker* and *Wolfgang Demuth*[*]

Decomposition of diethyl ether by alkyllithium compounds primarily occurs according to eq. (1)[1]. α-Elimination has been discussed as the mechanism of this reaction, by analogy with findings for dimethyl ether, but this has not been proved[1]. We recently observed that the solution contains higher alkyllithium compounds soon after the beginning of the decomposition, these being formed in a secondary reaction[2] whereby the ethylene produced is partially inserted into the lithium-carbon bond of still unused organolithium compound [eq. (2)].

$$RLi + (C_2H_5)_2O \rightarrow RH + CH_2{=}CH_2 + LiOC_2H_5 \quad (1)$$

$$RLi + n CH_2{=}CH_2 \rightarrow R(CH_2{-}CH_2)_nLi \quad (2)$$

In principle, three mechanisms have to be considered for the primary step in the decomposition of diethyl ether by organometallic compounds: α-elimination as for dimethyl[1] and butyl methyl ether[1,3], β-elimination as for methyl 1-methylheptyl ether[4] and finally α', β-elimination



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as for benzyl ethyl ether[5, 6]. All three mechanisms would lead to the same products from diethyl ether [eq. (3)], so it is not remarkable that for this ether cleavage both β-elimination[7] and primary metalation at the α-position[8] have been discussed, and recently even α', β-elimination[9].

To clarify the cleavage mechanism we have synthesized both the specifically α- and the specifically β-labeled diethyl ether in high purity and yields of up to 80%, using a specially developed apparatus[10]. In order to be able to follow the reaction by NMR spectroscopy we chose perdeuterioethyllithium as the organometallic component, which we prepared in our microapparatus[11] directly in the NMR tube from C_2D_5Br and lithium powder under argon at −35 °C in α- or β-deuterated diethyl ether. When cleavage was complete we hydrolyzed the products and studied them additionally by gas chromatography and by mass spectrometry.

It was found that α-deuterated diethyl ether was cleaved by perdeuterioethyllithium as fast as the undeuterated ether, and that this occurred by β-elimination. The ethylene produced, which had reacted almost quantitatively according to eq. (2), must have been exclusively $CH_2{=}CD_2$, as was shown by the broadened singlet signals at $\tau = 11.0$ ($-CD_2CH_2Li$) and 8.7 ($-CH_2CD_2Li$), so that α-elimination is excluded from consideration [eq. (4)].

This was confirmed by the mass spectra of the hydrocarbons produced by the cleavage—they consisted to more than 99% of *n*-alkanes with an even number of C atoms and mass numbers $[35 + n \cdot 30]$ ($n = 1$ to 12). The hydrocarbons $C_2D_5(C_2D_2H_2)_nH$ up to eicosane ($n = 9$) were also detected by gas chromatography. The alcohol obtained after hydrolysis in the aqueous phase was doubly deuterated; the appearance of worthwhile amounts of $CH_3CDHOLi$ and thus α',β-elimination were already excluded by NMR spectroscopy.

$$C_2D_5Li + (CH_3CD_2)_2O \xrightarrow{\beta} C_2D_5H + CH_2{=}CD_2 + CH_3CD_2OLi$$
$$\xrightarrow{\alpha} C_2D_6 + CH_2{=}CDH + CH_3CD_2OLi \quad (4)$$
$$\xrightarrow{\alpha',\beta} C_2D_6 + CH_2{=}CD_2 + CH_3CDHOLi$$

$$C_2D_5Li + (CD_3CH_2)_2O \xrightarrow{\beta} C_2D_6 + CH_2{=}CD_2 + CD_3CH_2OLi$$
$$\xrightarrow{\alpha} C_2D_5H + CD_2{=}CDH + CD_3CH_2OLi \quad (5)$$
$$\xrightarrow{\alpha',\beta} C_2D_5H + CH_2{=}CD_2 + CD_3CDHOLi$$

Because of the isotope effect[12], cleavage of the β-deuterated diethyl ether occurs 4 to 5 times more slowly (4 months at 35 °C), three mechanisms coming simultaneously into play [eq. (5)]. The cleavage occurs this time predominantly by an α',β-mechanism (55—60%), and the β-elimination, at *ca.* 35%, retreats far into the background. Of particular interest is the finding that 5—10% of α-elimination also occurs; this is proved by the fact that an average of one in about every ten ethylene molecules that are inserted into the lithium-carbon bond according to eq. (2) has a mass of 31 ($CD_2{=}CDH$). α- and α',β-Elimination together are about twice as strongly represented as β-elimination, since C_2D_5H and C_2D_6 are found in approximately 2:1 proportions[12].

Competitive experiments with 1:1 mixtures of, on the one hand, α- and β-deuterated diethyl ether (the α-deuterated ether being almost exclusively attacked by the perdeuterioethyllithium) and, on the other hand, of α-deuterated and undeuterated diethyl ether (the two ethers being attacked to the same extent) showed that the undeuterated ether was cleaved, like the α-deuterated ether, by β-elimination. The experiments, however, do not permit a decision whether these reactions involve only ionic processes or whether radical mechanisms also come into play. Kinetic measurements and investigations of other ethers are in progress.

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[12] We thank Dr. *D. Krauss*, Heidelberg, for the quantitative mass-spectrometric analysis of the gaseous reaction products.

Synthesis of 8,8'-Biheptafulvenyl

By *Shigeyasu Kuroda, Masaji Oda*, and *Yoshio Kitahara*[*]

We report here the synthesis of 8,8'-biheptafulvenyl which is a higher analog of heptafulvalene.

Heating ethyl 7-cycloheptatrienecarboxylate *(1)*[1] under reflux in xylene for 5 h gave the 1,5-sigmatropic hydrogen shifted product, the carboxylate *(2)* (contaminated with about 5% of 1-ester). Reduction of *(2)* with $LiAlH_4$ gave the alcohol *(3)* (b.p. 66—67 °C/1 torr) in high yield. This was easily converted into the corresponding bromide *(4)* (b.p. 69—72 °C/2 torr) in 63% yield by treatment with excess concentrated hydrobromic acid in an ice bath. Treatment of *(4)* with magnesium in ether resulted in

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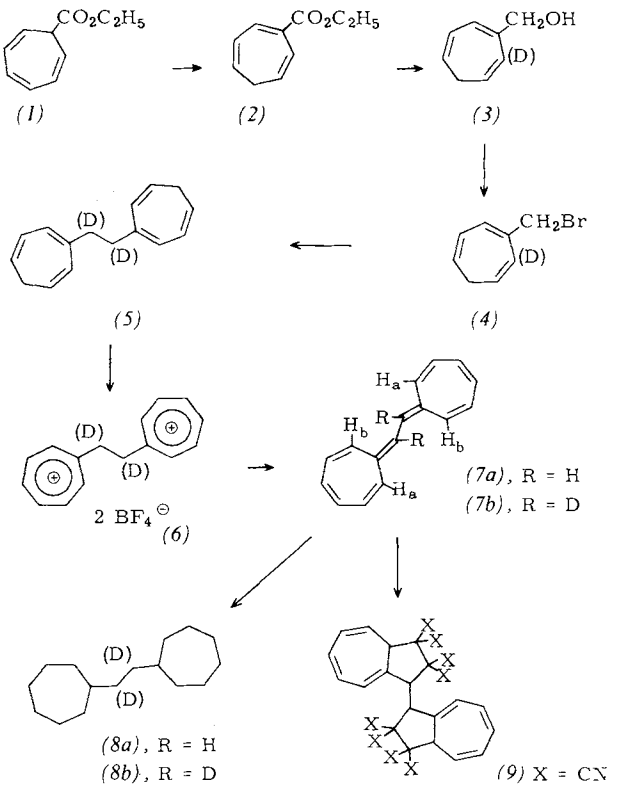
coupling to produce 1,2-di(3-cycloheptatrienyl)ethane *(5)* (b.p. 107—110 °C/0.2 torr, *m/e* 210) in 85% yield. Hydride-abstraction from *(5)* with triphenylmethyl tetrafluoroborate (2 equiv.) in dichloromethane afforded the corresponding salt *(6)* (m.p. 228—230 °C, 60% yield), whose structure was confirmed by the ^{1}H-NMR spectrum [60 MHz, in CF_3COOH, TMS, $\delta = 9.33$ (m), and 4.08 ppm (s), ratio 3:1].



8,8'-Biheptafulvenyl *(7a)* was easily obtained from *(6)* in 46% yield by cleavage of dehydrofluoroboric acid with triethylamine in dichloromethane. The dideuterio derivative *(7b)* could be obtained in the same way by using $LiAlD_4$. *(7a)* and *(7b)* can be isolated by chromatographing the concentrated reaction mixture through a short silica-gel column. Solid *(7a)* and *(7b)* decompose completely within one day in air at room temperature; they are, however, moderately stable in carbon tetrachloride solution and remain unchanged after one day. Compound *(7a)* crystallizes from *n*-hexane-dichloromethane at 20 °C as red brownish needles, m.p. 120—121 °C; *m/e* = 206 (M^+), 128, 115, 103, 91, and 78; IR (KBr): $\nu_{max} = 3010$ w, 1573 s, 924 m, 878 m, 744 s, and 720 cm^{-1}; UV (cyclohexane): $\lambda_{max} = 242$ (log $\varepsilon = 4.20$), 412 (4.61), and 438 nm (4.54). The intense absorption in the visible spectrum lies at about 65 nm longer wavelength than that of heptafulvalene (7,7'-bicycloheptatrienylidene)[2, 3].

The NMR signals of the ring protons of *(7a)* (Fig. 1) at $\delta \approx 5.3$ ppm appear close to those of 8-vinylheptafulvene (*ca.* 5.4)[3]; heptafulvalene absorbs at 5.91 ppm[2, 3]. In the NMR spectrum (100 MHz) of *(7b)*, the signal at $\delta = 5.39$ ppm has disappeared. The structured doublet at 5.95 and 5.70 ppm can be assigned to H_a and H_b, respectively. H_a may be more strongly deshielded by the other heptafulvene group in the molecule than H_b. In view of the large steric interaction of the two rings in the cisoid form, compound *(7)* may preferably exist in transoid form at room temperature.

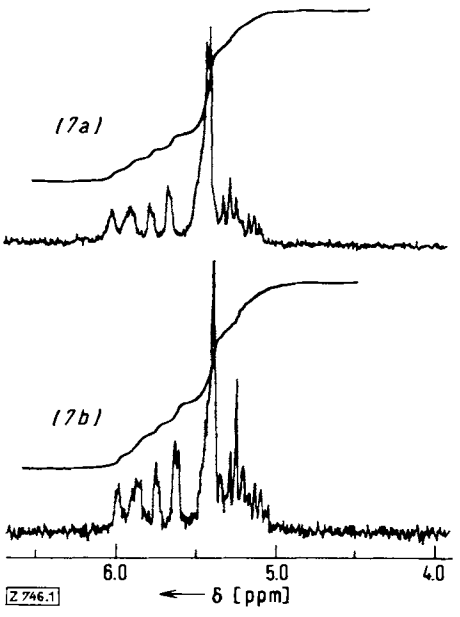


Fig. 1. 100-MHz ^{1}H-NMR spectrum (in CCl_4) of 8,8'-biheptafulvenyl *(7a)* and 8,8'-dideuterio-8,8'-biheptafulvenyl *(7b)*.

Complete hydrogenation of *(7a)* and *(7b)* on platinum oxide catalyst gave *(8a)* (*m/e* = 222) and *(8b)* (*m/e* = 224), respectively. *(7a)* easily reacts with two moles of tetracyanoethylene in dichloromethane at room temperature to give a pale yellow mixture of cycloadducts, which could not be separated. UV (268 nm) and ^{1}H-NMR spectrum of the mixture (60 MHz, $CDCl_3$, $\delta = 6.6$ (m), 5.7 (m), 4.3 (m), and 3.2 (m) in the ratio 4:1:1:1) suggest that it consists of stereoisomers of 8 + 2 cycloadducts *(9)*.

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[1] *K. Conrow*, J. Amer. Chem. Soc. *81*, 5461 (1959).

[2] *J. R. Mayer*, Ph. D. Dissertation, Yale University; *W. von E. Doering*: Theoretical Organic Chemistry. The Kekulé Symposium. Butterworth, London 1959, p. 35.

[3] *D. J. Bertelli, C. Golino*, and *D. L. Drever*, J. Amer. Chem. Soc. *86*, 3329 (1964).

Reactions of Carbonylmetal Hydrides with Aziridine and Propylene Sulfide (2-Methylthiirane)[1]

By *Wolfgang Beck, Wolfgang Danzer*, and *Roland Höfer*[*]

Treating tetracarbonylhydridocobalt with oxirane leads to tetracarbonyl-(2-hydroxyethyl)cobalt or -(3-hydroxypropionyl)cobalt[2]. Reaction of aziridine with the carbonyl hydrides $HMm(CO)_5$, $HMn(CO)_4PPh_3$, and $HM(CO)_3(\pi\text{-}C_5H_5)$ (M = Mo or W) leads to formation of 3-aminopropionyl chelate complexes[3] according to the reaction scheme.

These reactions can be regarded formally as 1,3-insertion of aziridine into the metal-H bond, it being assumed that a 2-aminoalkyl complex arises by protonation of the nitrogen and ring opening; subsequently the alkyl group migrates to the CO ligand and the amino group becomes bonded to the metal.

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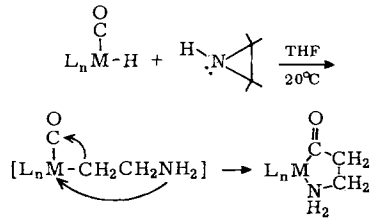
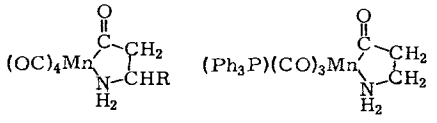
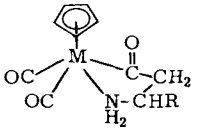




(1a), R = H
(1b), R = CH_3

(2)



(3a), M = Mo, R = H
(3b), M = Mo, R = CH_3
(3c), M = W, R = H
(3d), M = W, R = CH_3

The structure of *(1)*, *(2)*, and *(3)* as 3-aminoacyl chelate complexes follows from the IR spectra (Table 1). The complexes *(3)* show the expected two ν(M)—C≡O bands; the IR spectra of *(1a)* and *(1b)* contain the four νCO vibrations required for octahedral *cis*-$M(CO)_4L_2$ complexes. Three stereoisomers (of which one is dissymmetric) are possible for *(2)*, but they cannot be distinguished unambiguously on the basis of the IR spectrum. The amino and the keto groups are characterized by the absorptions at 3300 ($\nu_{as}NH_2$ and ν_sNH_2) and 1600 cm^{-1} (ν>C=O and δNH_2). Complexes of the same type have been obtained by *King et al.*[4] by a different route, from (2-chloroethyl)-dimethylamine and carbonylmetalates.

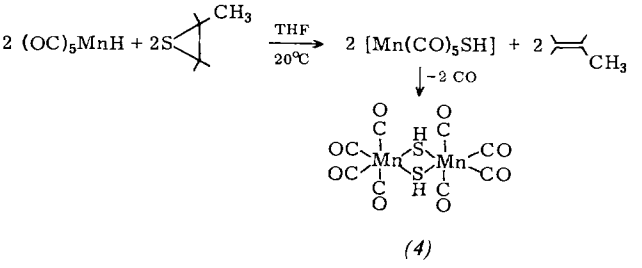
The compounds *(3)* deserve particular attention, as they are dissymmetric owing to the aminoacyl ligands. In *(3b)* and *(3d)* the aminoacyl ligand contains an additional chiral center at a C atom, so that two diastereoisomeric pairs could be formed. The occurrence of only one doublet for the methyl protons in the ^{1}H-NMR spectrum of *(3b)* and *(3d)* indicates that only one pair of enantiomers (DD,LL) is formed. Optically active compounds of the type π-$C_5H_5Mo(CO)_2$(L-L') with other chelate ligands were recently separated by *Brunner et al.* into their optical antipodes[5].

Table 1. IR absorptions (cm^{-1}) of aminopropionyl chelate complexes.

	ν(M)—C≡O [a]	νNH_2 [b]	ν>C=O, δNH_2 [b]
(1a)	2067m, 1980sh, 1964s, 1945s	3310m, 3250m	1622m, 1577m
(2)	2008m, 1915s, 1900sh	3300w, 3260w	1622m, 1596m
(3a)	1935s, 1847s	3312m, 3240m	1598m, 1545m
(3c)	1938s, 1847s	3295m, 3215m	1600m, 1532m

[a] Solution in CH_2Cl_2.
[b] Solid in KBr.

Propylene sulfide (2-methylthiirane) reacts with pentacarbonylmanganese in a "desulfurization reaction" with insertion of sulfur into the Mn—H bond, yielding *(4)* which is a dimeric SH-bridged complex:



(4)

Octacarbonyl-di-μ-hydrogensulfidodimanganese *(4)* (point group D_{2h} with SH as a point mass) is the first complex containing SH bridges and, like the corresponding phenylthio complex $[Mn(CO)_4SPh]_2$[6], shows four νCO bands (2077, 2018, 2004, 1972 cm^{-1}; solution in CCl_4). The observed three νSH (2571, 2531, 2481 cm^{-1}) or νSD bands (1867, 1841, 1806 cm^{-1}; solid in KBr) indicate the presence of *syn*- and *anti*-isomers (*syn* and *anti* refer to the position of the H atoms). In the mass spectrum of *(4)* the complete series of ions $H_2S_2Mn_2(CO)_n^+$ (n=0—8), $HS_2Mn_2^+$, $S_2Mn_2^+$, SMn_2^+, Mn_2^+ can be observed, as expected.

The reaction of $HMn(CO)_5$ with *trans*-2,3-dimethylthiirane (*trans*-2,3-butene sulfide) affords only *trans*-2-butene alongside *(4)*, *i.e.* the two C—S σ-bonds of the three-membered ring are opened concertedly (cheletropic reaction)[7], as in the stereospecific transfer of sulfur from butene sulfides to phosphanes.

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German version: Angew. Chem. *85*, 87 (1973)

[1] Part 1 of Reactions of Hydrido Complexes with Strained Heterocycles.

[2] *R. F. Heck*, J. Amer. Chem. Soc. *85*, 1460 (1963).

[3] $HCo(CO)_4$ also reacts with aziridine in tetrahydrofuran, yielding aminopropionyl complexes, and removal of the chelate ligand (*e.g.* by H^+ or H_2/CO) is at present under investigation.

[4] *R. B. King* and *M. B. Bisnette*, Inorg. Chem. *5*, 293 (1966).

[5] *H. Brunner* and *W. A. Herrmann*, Angew. Chem. *84*, 442 (1972); Angew. Chem. internat. Edit. *11*, 418 (1972).

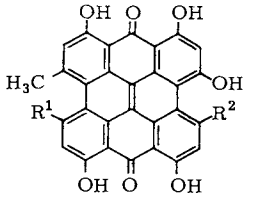
[6] *W. Hieber* and *W. Schropp jr.*, Z. Naturforsch. *14b*, 460 (1954).

[7] *R. B. Woodward* and *R. Hoffmann*, Angew. Chem. *81*, 797 (1969); Angew. Chem. internat. Edit. *8*, 781 (1969); *D. B. Demsey* and *M. J. Boskin*, J. Amer. Chem. Soc. *82*, 4736 (1960).

Alkaline Condensation of Emodin to Isohypericin: A Simple Synthesis of the *meso*-Naphthodianthrone (Phenanthro[1,10,9,8-*opqra*]perylene) System[**]

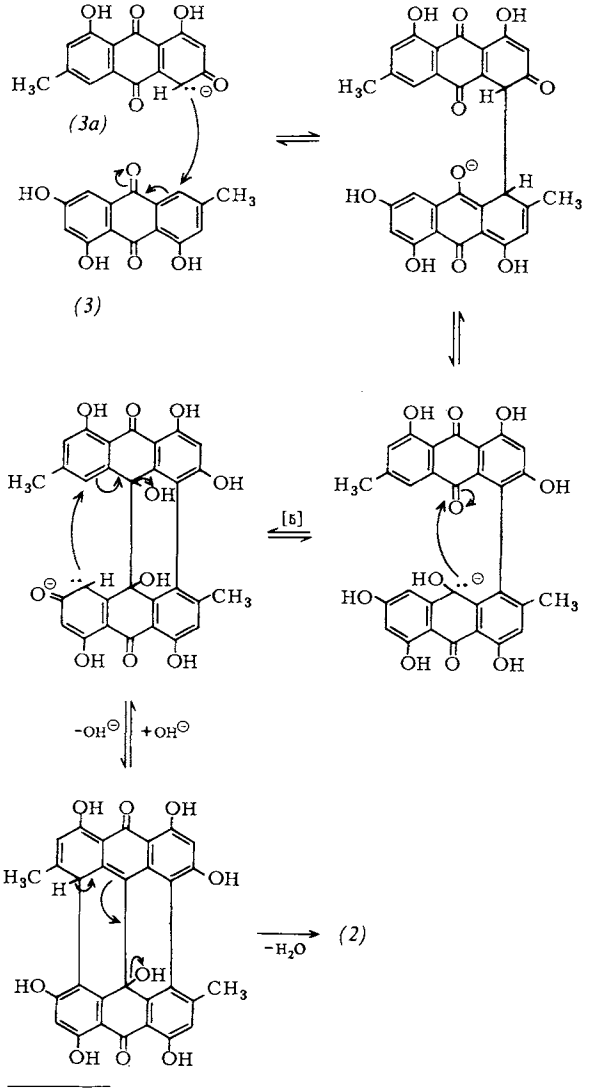
By *Wolfgang Steglich* and *Rüdiger Arnold*[*]

In their work on the structure of hypericin *(1)*, *Brockmann et al.*[1] discussed the possibility that "isohypericin" *(2)* might be formed alongside *(1)* in the oxidative dimerization of emodin-9-anthrone. We have now found that *(2)* is accessible in a facile manner from emodin *(3)*.



(1), $R^1 = CH_3$, $R^2 = OH$
(2), $R^1 = OH$, $R^2 = CH_3$

If *(3)* (0.5 mmol) is heated with hydroquinone (1 mmol) in 0.6 N KOH (3 ml) under nitrogen in a sealed tube for 3 weeks at 110 °C, dark-violet crystals can then be isolated in 35% yield by acidification, extraction with ethyl acetate, and chromatography on cellulose powder with ethyl acetate/acetone (1:1) as eluant. These crystals give red solutions in pyridine or methanol that, like those of *(1)*, exhibit intense red fluorescence. This compound is not to be distinguished from authentic *(1)* by thin-layer chromatography[2]. Since the absorption spectra of the two compounds in methanol, THF, and concentrated sulfuric acid are very similar, but differ in alkaline media[3], our compound can only be isohypericin *(2)*. This is confirmed by the mass spectrum of the orange-yellow hexaacetate which, starting from the molecular ion $m/e = 756$, shows six consecutive losses of ketene. If the synthesis of *(2)* is effected without addition of hydroquinone, then 2,5'-bisemodin and traces of norxanthorin[4] are formed as by-products.



The reaction conditions exclude an oxidative coupling step in the formation of the *meso*-naphthodianthrone system. Its appearance is explained without difficulty if Michael addition of an emodin anion *(3a)* to a molecule of emodin *(3)* is assumed as the primary step, followed by a series of simple tautomerizations, condensations, and eliminations.

We are now studying the application of the new *meso*-naphthodianthrone synthesis to simpler hydroxyanthraquinones.

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[1] *H. Brockmann, E. H. v. Falkenhausen, R. Neeff, A. Dorlars,* and *G. Budde*, Chem. Ber. *84*, 865 (1951).

[2] $R_F = 0.40$ on silica gel plates F 254 (E. Merck, Darmstadt), with benzene/ethyl formate/formic acid 13:5:4 as eluant.

[3] In the dianion of *(1)* there is strong interaction between the two neighboring β-phenolate groups, and this is not present in *(2)*.

[4] *R. Arnold*, forthcoming Dissertation, Technische Hochschule München.

[5] *K. Bredereck, L. Banzhaf,* and *E. Koch*, Chem. Ber. *105*, 377 (1972), recently reported the condensation of substituted anthrahydroquinones with formaldehyde to give 10-hydroxy-10-(hydroxymethyl)-9-anthrones.

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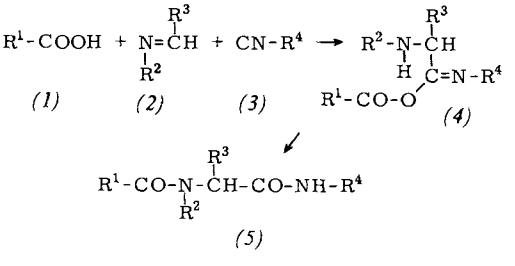
[**] We thank the Deutsche Forschungsgemeinschaft for supporting this work, and Prof. *H. Brockmann* (Göttingen) for a sample of hypericin.

Stable α-Addition Products of Four-Component Condensation

By *Dieter Marquarding*[*]

In four-component condensation[**] of Ugi type[1], carboxylic acids *(1)* react with aldimines *(2)* and isocyanides *(3)* to give α-(acylamino) amides *(5)*. The α-addition



(1) *(2)* *(3)* *(4)* *(5)*

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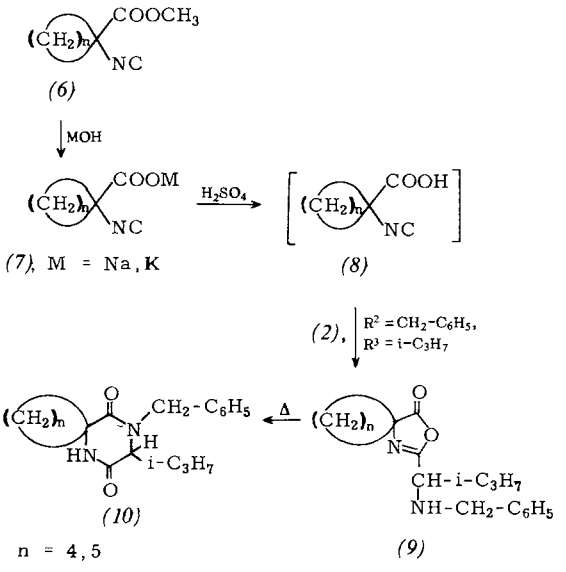
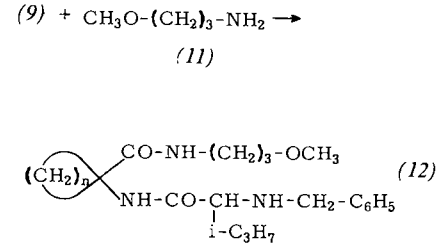
[**] Four components are obtained if the aldimine is regarded as the product from aldehyde and amine.

products *(4)* are assumed to be intermediates that undergo stabilization by rearrangement to *(5)*. We have now been able to isolate such α-adducts as stable compounds.

The readily accessible[2] 1-isocyanocycloalkanecarboxylic esters *(6)* can be easily hydrolyzed to the water-soluble salts *(7)*, which are fairly stable even in the solid state[3]. If the alkaline aqueous solution of *(7)* is neutralized by a mineral acid in the presence of an aldimine *(2)* (*e.g.* R^2 = benzyl, R^3 = isopropyl) and the mixture is then at once shaken with an inert water-immiscible solvent, the product *(9)* is obtained. If *(2)* is added only after the neutralization, then *(9)* is not formed.



The free 1-isocyano carboxylic acid *(8)* could not be isolated, but it is reasonable to assume that it is formed as an intermediate and undergoes four-component condensation with the aldimine *(2)*. Here the α-adduct must be the azlactone *(9)*, a structure in accord with the physical data[4] (Table 1). Acylation to give *(10)* (Table 1) proceeds only in the melt but then occurs almost quantitatively. Not only the intramolecular acylation of *(9)* to give *(10)*, but also the acylation of the primary amine *(11)* by *(9)* to give *(12)*, are further confirmation of the structure assumed for *(9)* [*(12)*, $n=4$, m. p. 80—81 °C; *(12)*, $n=5$, m. p. 74—75 °C; both from light petroleum]. *(9)* does not react with *tert*-butylamine in benzene solutions even on prolonged boiling, possibly due to steric hindrance.



The structure of *(12)* was confirmed both by IR and NMR data and by independent synthesis by four-component condensation of *N*-benzylvaline (as ammonium salt[5]), cyclopentanone, or cyclohexanone, and 1-isocyano-3-methoxypropane.

The remarkable stability of *(9)* can be ascribed to its spiro structure, since analogous azlactones without spiro structure (*e.g.* from 2-isocyano-2-methylpropionic acid) are indeed formed (strong band at 1810 cm^{-1}) but decompose on attempted isolation.

Table 1. Properties of compounds of types *(9)* and *(10)*.

Cpd., m.p. [°C]	Yield [%]	IR [cm^{-1}] NH	Azlactone	C=N	^{1}H-NMR, δ [ppm] C_6H_5	CH_2Ph	CH-iPr	ring NH	$CH(Me)_2$	$(CH_3)_2CH$
(9), $n=4$	15	3305	1865 (w)	1665 (s)	7.32	3.76 [b]	3.18	1.96, 2.07		1.00, 0.93,
61–63 [a]			1815 (s)		(s)	$J_{gem}=13.0$	6.7 (d)	(m)	(s)	6.5 (d), 6.5 (d)
			1770 (w)		5 H	2 H	1 H	10 H		6 H
(9), $n=5$	77	3290	1812 (Sh)	1670 (s)	7.31	3.78 [b]	3.19,	1.70, 2.00		1.19, 0.96
66.5–68 [a]			1815 (s)		(s)	$J_{gem}=13.0$	6.7 (d)	(m)	(s)	6.5 (d), 6.5 (d)
			1885 (w)		5 H	2 H	1 H	12 H		6 H

Cpd., m.p. [°C]	Yield [%]	IR [cm^{-1}] NH	C=O	^{1}H-NMR, δ [ppm] C_6H_5	NH	CH_2Ph	CH-iPr	ring $CH(Me)_2$	$(CH_3)_2CH$
(10), $n=4$	90	3190	1675 (s)	7.24	≈7.75	5.48, 3.90, 3.71		≈1.8, ≈2.2	1.13, 1.00
144 [c]		(br.)	1645 (s)	(s)	(br.)	$J_{gem}=15.0$	4.0 (d)	(m)	7.0 (d), 7.0 (d)
				5 H	1 H	1 H	2 H	9 H	6 H
(10), $n=5$	90	3200	1675 (s)		7.27	5.47; 3.92, 3.72,		≈1.6, ≈2.2	1.13, 1.00
170–173 [c]		(br.)	1655 (s)		(s)	$J_{gem}=15.0$	4.0 (d)	(m)	6.9 (d), 6.9 (d)
			1638 (s)		6 H	1 H	2 H	11 H	6 H

[a] From light petroleum.
[b] δ-Value around which the AB quartet is grouped. The separation of the inner lines is 3.5 Hz. J_{gem} is of the order of Δδ.
[c] From methanol.

[1] *G. Gokel, G. Lüdke,* and *I. Ugi* in *I. Ugi:* Isonitrile Chemistry, Academic Press, New York 1971, p. 145, and literature cited therein.

[2] *I. Ugi, U. Fetzer, U. Eholzer, H. Knupfer,* and *K. Offermann,* Angew. Chem. *77*, 492 (1965); Angew. Chem. internat. Edit. *4*, 472 (1965); in *W. Foerst:* Neuere Methoden der präparativen organischen Chemie. Verlag Chemie, Weinheim 1966, Vol. II, p. 37.

[3] D. Marquarding, unpublished work (1969).

[4] For IR data see *E. Schnabel,* Liebigs Ann. Chemie *688*, 238 (1965).

[5] *I. Ugi* and *C. Steinbrückner,* Chem. Ber. *94*, 2802 (1961).

2'-(1-Benzylamino-2-methylpropyl)cyclohexanespiro-4'-oxazolin-5'-one (9), n=5

Compound *(6)* (0.01 mol, $n=5$) is dissolved in 1N sodium hydroxide solution (30 ml), a layer of chloroform is placed under the clear solution, and *(2)*, R^2 = benzyl, R^3 = isopropyl (0.02 mol), is added. The mixture is well shaken and neutralized with 2N sulfuric acid. The chloroform layer is separated, dried, and evaporated in a vacuum. The residue is purified over silica gel (Merck, 0.05—0.2 mm; light petroleum/ethyl acetate 10:1).

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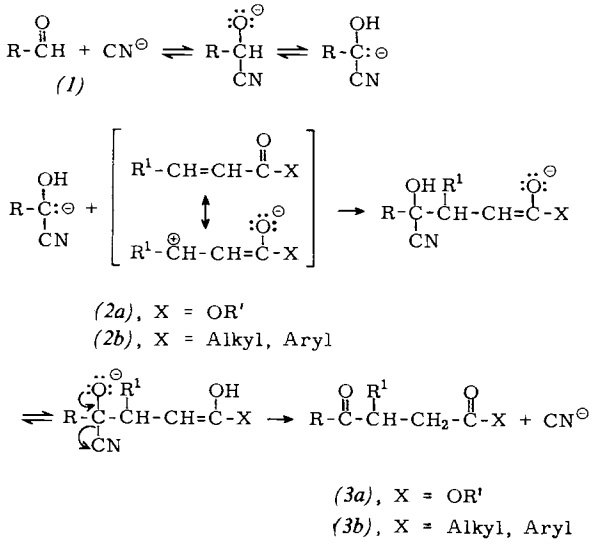
A New Method for Addition of Aldehydes to Activated Double Bonds

By *Hermann Stetter* and *Manfred Schreckenberg*[*]

Radical addition of aldehydes to α,β-unsaturated carbonyl compounds is a known process[1], but only in rare cases are the results preparatively favorable.

We have found aldehydes *(1)* to add smoothly to α,β-unsaturated carboxylic esters *(2a)*, ketones *(2b)* or nitriles under the catalytic influence of cyanide ions, whereby γ-oxo carboxylic esters *(3a)*, γ-diketones *(3b)* or γ-oxo nitriles are respectively formed.



(2a), X = OR'
(2b), X = Alkyl, Aryl

(3a), X = OR'
(3b), X = Alkyl, Aryl

The reaction can be carried out in polar solvents such as dimethylformamide and dimethyl sulfoxide. In the examples tabulated the reaction conditions were maintained as follows:

A solution of the unsaturated carbonyl compound or the corresponding nitrile (0.5 mol) in dimethylformamide (100 ml) is dropped with stirring into a solution of the aldehyde (0.5 mol) and sodium cyanide (0.1—0.5 mol) in dimethylformamide (150—250 ml) at *ca.* 35 °C, but in the case of acrylonitrile an excess of 0.35 mol is advantageous. The mixture is stirred until reaction is complete (1—4 h). Working up may be by pouring into water and extraction with chloroform.

Table 1. Examples of the reaction of aromatic aldehydes with α,β-unsaturated carbonyl compounds or nitriles:

$$R{-}CHO + R^1{-}CH{=}CH{-}R^2 \rightarrow R{-}CO{-}CHR^1{-}CH_2{-}R^2$$

R	R^1	R^2	M.p. [°C] B.p. [°C/torr]	Yield [%]
C_6H_5	H	CN	76	80
C_6H_5	CH_3	$COOC_2H_5$	119–121/0.5	33
C_6H_5	$COOC_2H_5$	$COOC_2H_5$	150–155/0.8	32
C_6H_5	C_6H_5	$COCH_3$	60–61	67
p-Cl—C_6H_4	H	CN	73	70
p-Cl—C_6H_4	CH_3	$COOC_2H_5$	34 [a]	56
p-Cl—C_6H_4	$COOC_2H_5$	$COOC_2H_5$	190/1.5	35
p-Cl—C_6H_4	C_6H_5	$COCH_3$	64	90

[a] B.p. 121 °C/0.2 torr.

Benzoins may replace benzaldehyde and Mannich bases may replace unsaturated ketones with equally good results. Table 1 contains some examples of the use of aromatic aldehydes. Examples with aliphatic and heterocyclic aldehydes will be published shortly.

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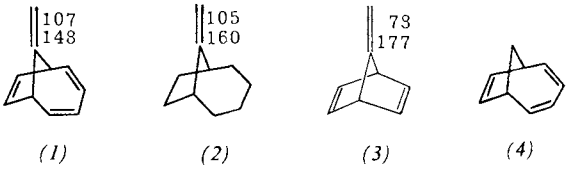
[1] *G. Sosnovsky*: Free Radical Reactions in Preparative Organic Chemistry. Macmillan, New York 1964, p. 125 ff.

Methylenebicyclo[4.2.1]nona-2,4,7-triene[1]

By *Manfred T. Reetz, Reinhard W. Hoffmann, Werner Schäfer*, and *Armin Schweig*[*]

We report here the synthesis and properties of methylenebicyclo[4.2.1]nona-2,4,7-triene *(1)* and 9-methylenebicyclo[4.2.1]nonane *(2)*. Starting from bicyclo[4.2.1]nona-2,4,7-trien-9-one[2] we obtained, by Wittig olefination in ether/THF followed by gas-chromatographic separation, a 44% yield of *(1)*: m.p. 29—32 °C; NMR (CCl_4), $\tau = 3.80$ to 4.36 m, 4.75 s, 5.33 s, 6.66 (d, $J = 6.5$ Hz) in relative intensities 2:1:1:1; IR, 3080, 2980, 1675, 1580, 1380 cm^{-1}; UV (cyclohexane), maxima at 265 nm (log $\varepsilon = 3.58$), 260 (3.59), 217 (3.57), shoulders at 275 (3.31), 245 (3.52). Compound *(2)* was prepared similarly from bicyclo[4.2.1]-nonan-9-one[2] in 37% yield: m.p. 42 °C; NMR (CCl_4), $\tau = 5.28$ s, 7.2—7.5 m, 7.8—8.9 m in relative intensities 1:1:6; IR, 2950, 2895, 1650, 1460, 1450 cm^{-1}



(1) *(2)* *(3)* *(4)*

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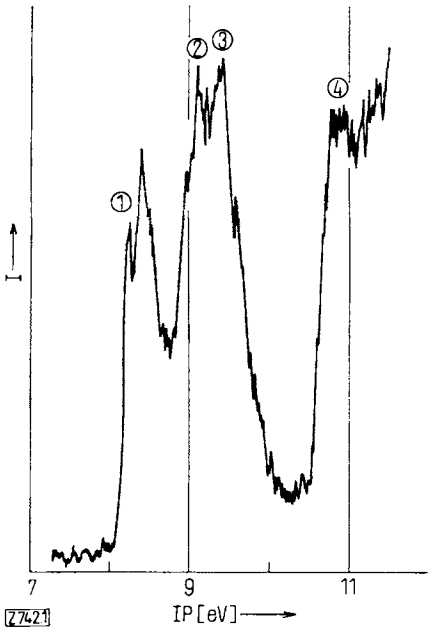

Fig. 1. Photoelectron spectrum [10] of methylenebicyclo[4.2.1]nona-2,4,7-triene *(1)*.

Compound *(1)* has three π-systems in spatial proximity of one another, these not being conjugated in the classical sense. Nevertheless, its photoelectron spectrum (Fig. 1) reveals some degree of interaction. Information about the energy levels of the "isolated" π-systems in *(1)* is provided by PE spectra of *(2)* and *(4)*[3]. From the correlation diagram (Fig. 2) it can be seen that the HOMO of the butadiene moiety in *(4)* appears energetically unchanged in *(1)* because its symmetry precludes coupling with the other π-systems. The correlation diagram also shows that the two MOs of the ethylene units in *(2)* and *(4)* accidently have the same energy and that their interaction in *(1)* leads to significant splitting. Here MINDO/2 calculations[4] lead to the assignment of π_2 in *(1)* as π-bonding and π_3 as π-antibonding, which indicates a predominant hyperconjugative (through bond[5]) interaction. A study of further models will have to precede a decision whether this bishomo-conjugative[6] interaction in *(1)* is accompanied by an additional, also symmetry-allowed interaction of π_3 with the symmetrical butadiene MO yielding a bicycloaromatic[7] system.

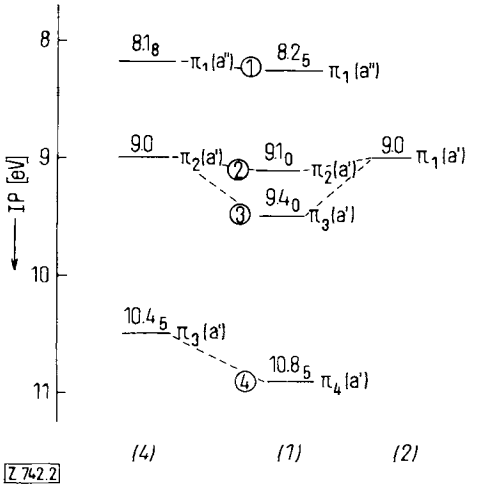

Fig. 2. Correlation diagram of the highest occupied MOs in bicyclo-[4.2.1]nona-2,4,7-triene *(4)*, methylenebicyclo[4.2.1]nona-2,4,7-triene *(1)* and 9-methylenebicyclo[4.2.1]nonane [2]. The numbers placed above the peaks are vertical ionization potentials. The MOs are classified according to the irreducible representations (*a''*, *a'*) of the C_s symmetry group.

Interaction of the π-systems could lead to polarization of the exocyclic double bond[8, 9]. We therefore studied the ^{13}C-NMR spectra of *(1)* and *(2)*. The difference in chemical shift (in ppm downfield from tetramethylsilane) between C-9 and C-10 was found to be 41 ppm for *(1)*. This difference is distinctly less than that for ω-methylenebicyclo[*n*.2.1]alkanes [50—60 ppm, cf. *(2)*], and the latter is in turn considerably smaller than that for *(3)* (99 ppm)[9]. The reason for this could be that the exocyclic double bond of *(1)*, in contrast to that of *(3)* gives up a small amount of its charge to the remainder of the π-system.

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[1] Part 17 of Theory and Application of Photoelectron Spectroscopy. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.—Part 16: *A. Schweig, U. Weidner*, and *G. Manuel*, J. Organometal. Chem., in press.

[2] *T. A. Antkowiak, D. C. Sanders, G. B. Trimitsis, J. B. Press*, and *H. Shechter*, J. Amer. Chem. Soc. *94*, 5366 (1972).

[3] *P. Bischof, R. Gleiter*, and *E. Heilbronner*, Helv. Chim. Acta *53*, 1425 (1970).

[4] *M. J. S. Dewar*: The Molecular Orbital Theory of Organic Chemistry. McGraw-Hill, New York 1969.

[5] *R. Hoffmann*, Accounts Chem. Res. *4*, 1 (1972).

[6] *S. Winstein*, Quart. Rev. Chem. Soc. *23*, 141 (1969).

[7] *M. J. Goldstein* and *R. Hoffmann*, J. Amer. Chem. Soc. *93*, 6193 (1971).

[8] The method of *Goldstein* and *Hoffmann* [7] does not lead to a clear prediction concerning the direction of polarization (if any) of the exocyclic double bond in *(1)*, since both a positive as well as a negative partial charge on C-9 could lead to a bicycloaromatic system.

[9] *R. W. Hoffmann, R. Schüttler, W. Schäfer*, and *A. Schweig*, Angew. Chem. *84*, 533 (1972); Angew. Chem. internat. Edit. *11*, 512 (1972).

[10] The He-I (584 Å) photoelectron spectra were measured with a PS-16 photoelectron spectrometer from Perkin-Elmer, Beaconsfield (England).

Biogenic Macromolecules of Arterial Tissue and Cartilage

By *Eckhart Buddecke*[*]

Proteoglycans are structural components of cells, of pericellular structures, and of the extracellular space in connective tissue. They have the chemical structure of graft polymers, in which polysaccharide chains are covalently linked to a central protein or polypeptide core. Chondroitin sulfate (CS), dermatan sulfate (DS), heparan sulfate, and keratan sulfate have been identified as polysaccharide components of proteoglycans of arterial tissue and cartilage.

Hyaline cartilage contains up to 40% of its dry weight of a proteoglycan whose carbohydrate content amounts to 84% and whose polysaccharide chains consist mainly of chondroitin sulfate $[(1\text{-}4)\beta$ GlcUA $(1\text{-}3)$GalNAc 4-sulfate$]_n$ bonded β-glycosidically to serine residues of the protein through the trisaccharide galactosylgalactosylxylosyl. Light scattering and viscosity measurements revealed a molecular weight of 0.5×10^6 to 1.0×10^6, the molecular shape of a stretched coil, a radius of gyration of 1400 Å, and an effective hydrodynamic volume of 200—400 ml of water per g. These figures were confirmed by electron micrographs showing an ellipsoidal molecular shape with a central protein filament of 1800—2000 Å length and 22 side chains of 520 Å length.

In a hybrid proteoglycan of arterial tissue, CS and DS are components of the same macromolecule and are present in part as copolymeric polysaccharide chains. The copolymeric structure of the polysaccharide chains was proved by isolation of a tetrasaccharide having the structure GlcUA—GalNAc sulfate—IdUA—GalNAc sulfate. On incubation of arterial tissue *in vitro* in the presence of ^{35}S-sulfate or ^{14}C-glucose, the ^{35}S or ^{14}C was incorporated into the polysaccharide chains at a constant rate for at least 6h; however, the specific radioactivity of the ester sulfate or iduronic acid groups of the DS is found to be 2—3 times greater than that of the ester sulfate or glucuronic acid groups of CS.

The chemical and metabolic heterogeneity of the polysaccharide chains of the hybrid CS—DS protein of arterial tissue is explained by the fact that biosynthesis of the carbohydrates is not subject to direct genetic coding but is controlled indirectly by the specificity and activity of the glycosyl transferases, by the substrate concentration, and by compartmenting of the pool of metabolic precursors. The metabolic heterogeneity of the copolymeric CS—DS chains is not in accordance with the generally assumed stepwise synthesis of the carbohydrate side chains of the proteoglycan molecules.

Their physicochemical properties enable the proteoglycans to bind water and Ca^{2+}. Further, in model experiments a "molecular sieve effect" could be observed: In solutions of critical concentration, proteoglycans form a gel-like macromolecular structure. Such systems are permeable to small molecules (glucose, amino acids) but inhibit the passage of larger molecules. *In vivo* this "molecular sieve effect" may be involved in control of extracellular and pericellular transport processes.

Lecture at Darmstadt on June 16, 1972 [VB 351 IE]
German version: Angew. Chem. 85, 94 (1973)

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Chemical Structure and Biological Action of the Components of Bee Venom

By *E. Habermann*[*]

Bee venom contains three types of active ingredient:

1. Histamine is the most important of the biogenic amines. It causes pain, dilates the blood vessels, and increases their permeability.

2. A group of biologically active peptides is responsible for the local and general toxicity of the venom. To this group belong:

a) *Melittin*, whose primary structure is

Gly—Ile—Gly—Ala—Val—Leu—Lys—Val—Leu—Thr—Thr—
—Gly—Leu—Pro—Ala—Leu—Ile—Ser—Trp—Ile—Lys—
—Arg—Lys—Arg—Gln—GlnNH_2

The extremely irregular distribution of its amino acid residues is remarkable. Mainly hydrophobic or slightly hydrophilic neutral groups occupy the positions 1 to 20 while the C-terminal portion is strongly basic and wholly hydrophilic. This structure resembles that of an invert soap. Both the hemolytic potency of melittin and its ability to lower the surface tension of water might be explained by its primary structure. This is in accord with the almost universal action of melittin on biological structures (cell membranes, mitochondria, lysosomes, liposomes) and on pharmacological test objects (smooth and striated muscle, neuromuscular junction, sensible nerve endings, tonus and permeability of blood vessels). Since mellitin constitutes about 50% of dried bee venom, this peptide can be considered as the principal toxin.

b) *Apamin* (2 to 4% of dried venom). Its sequence is

Cys—Asn—Cys—Lys—Ala—Pro—Glu—Thr—Ala—Leu—Cys—
—Ala—Arg—Arg—Cys—Gln—Gln—HisNH_2

The four half-cystines exist in the disulfide form. Unlike the action of melittin, that of apamin is highly specific, in that it augments the spinal polysynaptic reflexes. In mice its action lasts for several days (LD_{50} : 4 to 5 mg/kg).—

c) *MCD peptide* (2 to 4% of the whole venom) degranulates rat mast cells. The histamine released lowers the blood pressure and dilates the blood vessels.

3. Enzymes. a) The structure and mode of action of *bee venom phospholipase A* has been determined recently by

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Vernon and his colleagues[1]. b) The venom *hyaluronidase* differs appreciably from that of the hyaluronidases of other organs, *e.g.* of ox testicles.

Lecture at Giessen on June 27, 1972 [VB 355 IE]
German version: Angew. Chem. *85*, 47 (1973)

[1] *R. A. Shipolini, G. E. Callewaert, R. C. Cottrell,* and *C. A. Vernon,* FEBS Letters *17*, 39 (1971).

Absorption of Light by Organic Molecules in Electric Fields—Some New Applications

By *H. Labhart*[*]

It was shown in the introduction how the change in intensity of incident polarized light on application of an electric field to a solution allows the determination of the angle between the dipole moment and the optical transition moment to an excited state[1]. Here it is briefly mentioned how several other excited state properties can be derived.

The first example concerns interpretation of the n-π^* transition of α-diketones[2]. If only the direct overlap of the atomic n-orbitals is taken into account, one expects that each of the two observed n-π^* bands results from an overlap of two transitions polarized perpendicularly to each other. On the other hand, CNDO calculations lead to the prediction that the longest-wavelength n-π^* band is due to a single transition polarized perpendicularly to the dipole moment and the shorter-wavelength n-π^* band to a transition polarized parallel to it. Measurements of the influence of an electric field on the spectrum of camphor diketone confirm the predictions of the CNDO calculations and strengthen the view that indirect interaction through the σ-orbitals of the carbon atoms determines the coupling of the n-orbitals.

A second application concerns the energetic coupling of the partial chromophores of 9,9′-spirobifluorene (SBF) and of 7,7′-dinitro-9,9′-spirobifluorene-2,2′-diamine (ANSBF)[3]. From the spectra it can be concluded that there is very weak coupling of the partial chromophores in the region of the longest-wavelength bands, and from the influence of the field on the spectrum of ANSBF it is clear that the transition moment makes an angle of approximately 45° with the dipole moment. Hence it follows that the excitation must be considered as localized on the partial chromophores. By measuring the degree of polarization of the fluorescent light it is possible to determine the degree to which energy is transferred from the initially excited to the non-excited chromophore during the time from excitation to emission. From this information one can calculate that the coupling energy U for SBF is $U = 7 \times 10^{-5}$ eV and for ANSBF is $U = 4.1 \times 10^{-3}$ eV. Since U vanishes for the equilibrium state of SBF owing to symmetry, the experimental value must be ascribed to vibrational influences.

With the same vibrational amplitude a coupling energy about ten times greater would be expected for ANSBF. The discrepancy from the approximately 60-times greater value found can be explained as due to slight twisting, which is caused by their electrostatic interaction, of the chromophores from their perpendicular positions. Estimation of the effect of spiroconjugation gave a negligibly small contribution.

Lecture at Würzburg on June 30, 1972 [VB 349 IE]
German version: Angew. Chem. *85*, 47 (1973)

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[1] *H. Labhart*, Adv. Phys. Chem. *13*, 179 (1967)
[2] *W. Hug, J. Kuhn, K. Seibold, H. Labhart,* and *G. Wagnière*, Helv. Chim. Acta *54*, 1451 (1971).
[3] *H. Labhart, E. R. Pantke,* and *K. Seibold*, Helv. Chim. Acta *55*, 658 (1972).

ABSTRACTS

Reviews

Abstracts of selected progress reports and review articles

Sequencing of peptides with the aid of dipeptidyl aminopeptidase I from bovine spleen is reported by *P. X. Callahan, J. K. McDonald,* and *S. Ellis.* This enzyme, which shows relatively little amino acid specificity, cannot cope with *N*-terminal arginyl and lysyl residues or with the cleavage of proline bonds. The time course of cleavage is followed by paper chromatography for small peptides, whereas larger peptides are cleaved in an ultrafiltration cell whose membrane only permits passage of the resulting dipeptides which are then identified by thin-layer or column chromatography. Difficulties are circumvented by adding an alanyl residue to the *N*-terminal end of the peptide under study or by removing a residue; the resulting peptide affords the sequence in the form of other dipeptides. [Dipeptidyl Aminotransferase I: Application in Sequencing of Peptides. Fed. Proc. *31*, 1105—1113 (1972); 17 references]

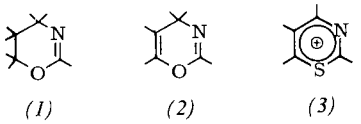
[Rd 545 IE—R]

Surface effects in hemostasis and thrombosis are considered by *E. W. Salzman.* In healthy individuals the blood circulates as a non-Newtonian fluid: however, contact with surfaces other than the endothelium of the blood vessels triggers off a complicated series of reactions which result in the formation of a "red clot" in stationary blood and a "white clot" in flowing blood. The latter phenomenon is designated thrombosis. Its significance is apparent from

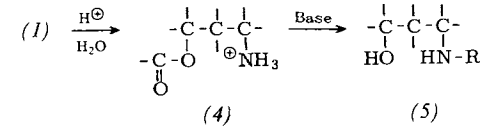
the fact that in the USA it ranks first among the causes of death. The article summarizes the present state of knowledge regarding the effects of "foreign" surfaces on the blood. [Surface Effects in Hemostasis and Thrombosis. Chem. Biosurfaces *2*, 489—522 (1972)]; 203 references]

[Rd 548 IE—G]

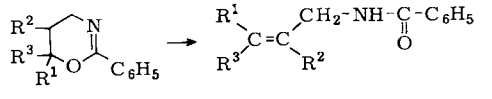
Derivatives of 1,3-oxazine and 1,3-thiazine are interesting intermediates for organic synthesis. *R. R. Schmidt* gives a survey of synthetic reactions for 5,6-dihydro-4*H*-1,3-oxazines *(1)*, 4*H*-1,3-oxazines *(2)*, and 1,3-oxazinium and 1,3-thiazinium salts *(3)*. Hydrolysis of *(1)* leads *via* 3-aminopropyl esters *(4)* to the stable 3-hydroxypropyl compounds *(5)*. Thermolysis of *(1a)* gives high yields of amidomethylation product *(6)*. 2-Alkyl- and 2-vinyl-substituted *(1)* react with organomethallic compounds to



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



(4) *(5)*



(1a) *(6)*

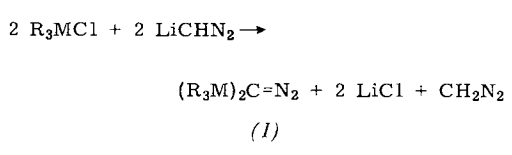
give strongly nucleophilic carbanions that permit numerous further reactions. Ring cleavages of system *(1)* lead to aldehydes and isocyanates. The oxazinium and thiazinium salts *(3)* are interesting intermediates for pyrazoles, 1,2-oxazoles, pyridine, pyrimidine, quinoline, and isoquinoline derivatives, 1,3-oxazines, unsaturated aldehydes, vinylogous quinone methides, *etc.*, nucleophilic attack being centered on C-6. [1,3-Oxazines and 1,3-Thiazines, Intermediates of Interest in Organic Synthesis. Synthesis *1972*, 333—350; 58 references]

[Rd 582 IE—M]

The occurrence and isotope distribution of xenon in terrestrial and extraterrestrial material, the concern of the new scientific discipline of xenology, is reviewed by *H. Hintenberger*. Xe, which has nine stable isotopes, offers more scope for the study of the early history of our solar system then any other element. The significance of Xe isotopes in these studies derives from the extremely sensitive methods available for its detection and the multiplicity of the possible nuclear reactions. Shifts in the abundances of the various Xe isotopes arise from fractionation processes (especially diffusion, and also condensation and evaporation processes) and from nuclear reactions, the abundance of only one isotope usually changing (radioactive decay, neutron capture, spallation reactions, fission of heavier elements). Lunar Xe exhibits considerable differences in isotope distribution compared to meteoritic Xe. The noble gases captured from the solar wind in lunar dust provide the most accurate information hitherto available regarding the noble gas abundances on the sun. [Xenon in irdischer und in extraterrestrischer Materie (Xenologie). Naturwissenschaften *59*, 285—291 (1972); 38 references]

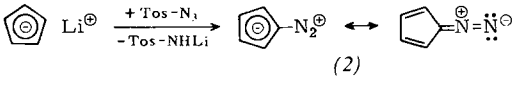
[Rd 584 IE—M]

Two new synthetic methods from diazo chemistry, *viz.* transformation of aliphatic diazo compounds with retention of the diazo group and reactions in which an azide group serves as diazo precursor, are dealt with in a review by *M. Regitz*. The first reaction can take place by nitration, halogenation, acylation, metalation, and substitution *via* metal derivatives *(1)*. Such substitutions are limited to diazomethyl compounds and a number of 1,1-disubstituted

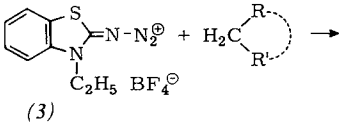


(1)

diazo alkanes. Other transformations are possible by addition of diazomethyl compounds to carbonyl compounds and electron-rich olefins, and by cleavage reactions, *e.g.* of diacyldiazomethanes to give acyldiazomethanes.— Diazo group transfer is conducted mainly with the stable and readily accessible tosyl azide. Reaction yields *e.g.* diazocyclopentadiene *(2)* and -cyclohexadiene, α-diazo carbonyl compounds, α-diazo sulfonyl compounds, α-diazo



(2)



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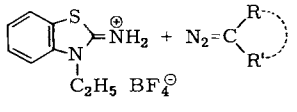
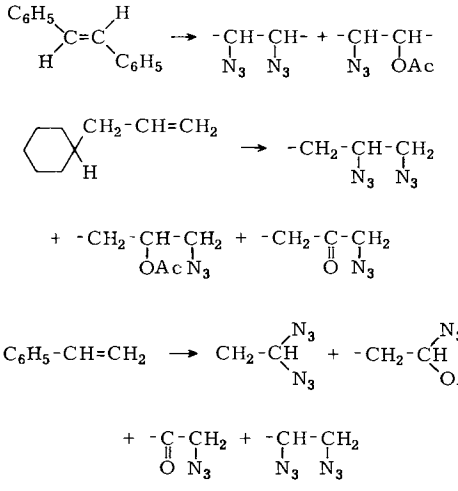


phosphono and α-diazo phosphinyl compounds. The preparative scope is considerably increased on use of azidinium salts *(3)*. [Recent Synthetic Methods in Diazo Chemistry. Synthesis *1972*, 351—373; 138 references]

[Rd 581 IE—M]

The reaction of olefins with lead(IV) acetate azides, $Pb(OAc)_{n-1}(N_3)_n$, *(1)*, a reagent discovered in 1969, is reviewed by *E. Zbira*. Compound *(1)* is produced by mixing $Pb(OAc)_4$ and $(CH_3)_3SiN_3$ in aprotic solvents at −40 to −20 °C. The olefins are added to one of the two components prior to mixing (−20 °C to room temperature). Depending on the kind of olefin, reaction yields diazido-, acetoxyazido-, and azido carbonyl compounds:



A large new range of possibilities open up in the steroid field. Bridged olefins (camphene, norbornene, benzonorbornadiene) undergo skeletal rearrangements. Triple bonds are also attacked by *(1)*, the temperature of reaction determining the product composition. The (diacetoxyiodo)-benzene/trimethylsilyl azide system reacts with olefins in a similar manner to *(1)*. [Organic Syntheses Using Lead(IV) Acetate Azides. Synthesis *1972*, 285—302; 74 references]

[Rd 583 IE—M]

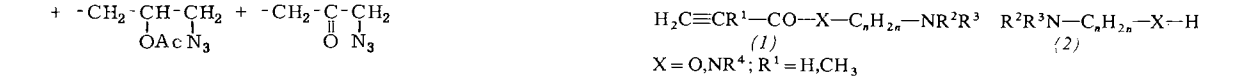
Patents

Abstracts of selected "Deutsche Offenlegungsschriften" (DOS), *i. e.* provisionally published specifications as filed with the German Patent Office

Thermosetting molding compositions consist of a polymerizable component A of a butadiene polymer having a high vinyl content and an isobutene polymer B. Components A that are regarded as particularly suitable are butadiene polymers containing at least 65% of 1,2-polymerized units. An average viscosity molecular weight of the polymer of between 500 and 500000 is preferred. The isobutene polymer used as component B serves to regulate the shrinkage that occurs during thermosetting. Solid, liquid, or rubbery materials having a number average molecular weight of between 1000 and 100000 may be used. The isobutene polymer may also contain an admixture of up to 15 wt.% of polymers of other monomers having C=C bonds, such as vinyl acetate, styrene, and isoprene. The concentration of the isobutene polymer is 1—50%, based on the weight of the butadiene polymer. [DOS 2136435; BP Chemicals Ltd., London]

[PR 9—E IE]

For the production of dyed objects from polylactones, *e.g.* polypivalolactone, a small quantity of ethylene copolymers containing tertiary N atoms is added to the polymers, the mixture is shaped, and the objects are dyed, optionally after acid treatment. The copolymers may be prepared *e.g.* from ethylene and amino esters or amino amides of acrylic or methacrylic acid *(1)* and optionally other comonomers, or may be obtained by chemical modification of copolymers of ethylene and esters of acrylic acid, methacrylic acid, maleic acid, or fumaric acid with tertiary amines *(2)*.



(1) *(2)*

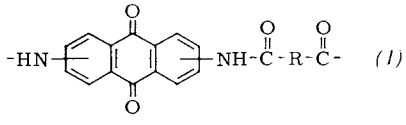
$X = O, NR^4$; $R^1 = H, CH_3$

R^2, R^3 = alkyl, cycloalkyl, aryl, aralkyl (C_1—C_8);
R^2 and R^3 may be connected together by one or more C, N, or O atoms;
$R^4 = H, R^2$; $n = 1$—4

The acid treatment can be carried out with acidic gases, mineral acids, carboxylic acids, halogen compounds liberating hydrogen halide on contact with water, boron trifluoride, esters of boric acid, and/or phenol. The dyeable plastics mixtures are characterized by higher stability during hot forming in comparison with those containing primary or secondary amino groups. [DOS 2143770; Shell Internationale Research Maatschappij N.V., Den Haag]

[PR 28 IE—C]

Quinonoid vat polymers characterized by the repeat structural unit *(1)*, where R is a bivalent aliphatic or aromatic

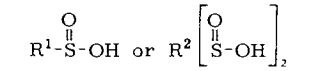


(1)

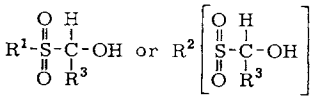
residue, are thermally very stable and are easy to process. The polymers can be dissolved by reduction (shortening) in aqueous alkali and converted into fibers, films, sheets, and coatings by reoxidation. The vat polymers are produced by polycondensation of diaminoanthraquinones with dicarboxylic acids and their amide-forming derivatives in solution or in substance at temperatures between room temperature and 350°C. [DOS 2056710; Battelle-Institut e.V., Frankfurt]

[PR 44 IE—E]

As a delayed-action accelerator for sulfur-vulcanizable rubber compositions one can use a) an organic sulfinic acid *(1)*, b) a metal salt or an amine salt of an organic sulfinic acid, or c) an aldehyde or aldehyde-amine derivative of an organic sulfinic acid *(2)*. R^1 denotes aryl, alkyl, cycloalkyl,



(1)



(2)

aralkyl, or alkaryl, R^2 denotes alkylene or arylene, and R^3 denotes hydrogen, alkyl, or aryl. Sulfinates of monovalent and bivalent metals may be used as metal salts, and salts with ammonia or primary, secondary, or tertiary amines as amine salts. The accelerators exhibit a high degree of safety against scorching when the mixing and processing operations are carried out at relatively high temperatures. [DOS 1 770905; Uniroyal, Inc., New York]

[PR 42 IE—E]

Shaped objects of nylon 4 that can be produced at temperatures well below the melting point of nylon 4 (polymer of 2-pyrrolidone) are obtainable by swelling nylon 4 with water and drying the swollen composition under pressure. The operation is carried out at a pressure of at least 3.5 kg/cm^2 and at a temperature of at least 25 °C, the temperature and the pressure being inversely related; lower temperatures are used at higher pressures, and higher temperatures at lower pressures. In this way, an integral structure is obtained without melting. Other materials such as wood pulp fiber, semisynthetic and synthetic fibers, and fillers may be blended with the swollen nylon 4. The shaped objects are produced by drying a nylon 4 pulp on a perforated support under pressure. [DOS 2142761; Alrac Corp., Stamford, Conn.]

[PR 43 IE—E]

BOOK REVIEWS

Gmelins Handbuch der anorganischen Chemie (Gmelin's Handbook of Inorganic Chemistry). 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., 8th fully revised edition.

System No. 14: Carbon, Part D 1. Carbon-Nitrogen Compounds. Principal editor: *Dieter Koschel.* 1971. vi, xxii, 475 pp., 51 figures, Balacron DM 574.—.

Whereas the volume "Carbon C" dealt with simple C—H compounds and the physical properties of CO, CO_2, and C_3O_2, the first volume of Part D is concerned with carbon-nitrogen compounds. In addition to the compounds of these two elements, compounds that also contain hydrogen and/or oxygen are included. The volume is thus of interest both to inorganic and to organic chemists, though this classification of chemists is as open to question as the classification of substances and their reactions into inorganic and organic chemistry. The principal editor refers in the foreword to the difficulties of selecting the compounds that should be treated predominantly from the standpoint of inorganic chemistry, corresponding to the character of the Handbook. With a few exceptions, the volume contains only C—N compounds having one C atom and their oligomers. These include $(CN)_{1,2,x}$, CN^-, N_3CN, C_4N_2, $C(CN)_2$, $CH(CN)$, $C_2(CN)_4$, HCN, HNC, H_2NCN, $(NH_2)_2CNCN$, $(CNO)_{1,2}$, HNCO, HOCN, NOCN, $(CN)_2CO$, urea, semicarbazide, and guanidine.

Among the compounds discussed, most space is devoted to cyanogen $(CN)_2$, hydrogen cyanide HCN, cyanamide H_2NCN, dicyanodiamide $(NH_2)_2C{=}NCN$, isocyanic acid HNCO, urea $(NH_2)_2CO$, and guanidine $(H_2N)_2CNH$. The treatment of cyanic acid HOCN, on the other hand, takes up only a few lines, since the free acid exists only as isocyanic acid, whereas HOCN molecules can be detected only on photolysis of HNCO in Ar and N_2 matrices. On the other hand the isomeric fulminic acid HCNO, with the structure of a nitrile oxide, is so stable that very thorough investigation of this substance has been possible. Cyanuric acid and its derivatives melamine, ammeline, and ammelide are also well known.

The form of the presentation should satisfy everyone. The only evidence of lack of systematic procedure is to be found in the description of the chemical behavior of the substances toward organic compounds. Though there is no denying the difficulty of drawing a boundary line just here and preserving the character of a handbook of inorganic chemistry, it would have been preferable to show more clearly the *connection* with organic chemistry in the classical sense. At isolated points, *e.g.* in the discussion of guanidine or of hydrocyanic acid, this has been achieved informatively, and yet without wasting space, by a few sentences and references to collective works on organic chemistry, but notes on behavior toward organic compounds are totally lacking in the discussion of very many other compounds (*e.g.* semicarbazide).

The literature has been evaluated up to and in some cases beyond the end of 1970, so that on grounds of current interest, Gmelin's "Carbon-Nitrogen Compounds" should not be lacking either in an inorganic or in an organic library.

System No. 49: Niobium, Part B2. Alloys. Principal editor: *Herbert Lehl.* 1971, vi, xvi, 307 pp., 167 figures, Balacron DM 382.—.

The present volume deals with alloys of niobium with metals of System Nos. 20 to 48 (lithium to vanadium). It comes between the first volume, which was published in 1970, and which deals with the compounds of niobium up to the element bismuth, and the just published volume B 3 in which the oxoniobates of the alkaline earth metals up to those of vanadium are discussed.

Alloys of niobium with the alkali metals are of no importance. Niobium is only slightly soluble in alkali metals. Solubility and corrosion are evidently decisively influenced by the impurities in the system in question, particularly by the oxygen content. On the other hand, the niobium-beryllium equilibrium diagram shows the existence of several intermetallic phases. Most niobium-beryllium alloys are characterized by extremely high melting points. According to present-day knowledge, the alloys of niobium with the other elements of the second main group and also of the second sub-group are of minor importance. Alloys of any desired composition can be prepared by fusion of niobium with aluminum. They are often superconducting,

and indeed their superconductivity is also the most intensively studied property of the other alloys discussed in this volume. Nb_3Al melt samples have jump temperatures between 17.3 and 18.5 °K. The extensively studied alloys of niobium with titanium belong to the class of "hard" superconductors, which correspond to the type III superconductors and can conduct high current densities without loss even in strong fields. However, these are also of interest because of their mechanical properties and because of the high chemical resistance of the niobium-rich alloys. A very similar class of materials, both in their superconductivity and in their mechanical properties, are the alloys of niobium and zirconium. Finally, considerable space is devoted to the descriptions of the binary Nb-Sn and Nb-V alloys. Niobium and lead are not miscible either in the molten state or in the solid state.

The literature has been evaluated up to and in some cases beyond mid-1970 for this volume.

System No. 46: Tin, Part B. The Element. Principal editor: *Gerhard Kirschstein.* 1971. vi, xix, 423 pp., 130 figures. Balacron DM 513.—.

Whereas Part A described the history and occurrence of tin, Part B deals with the element itself. Short introductory chapters on the position of the element in the periodic system and its atomic weight are followed by a longer chapter on its industrial production, which also includes the purification of crude tin and data on purity testing. Tables give figures for the world production up to 1968 and the tin consumption for various purposes in the USA. The next chapter deals with colloidal solutions and aerosols. Considerable space is devoted to the description of the preparation, separation, and enrichment of tin isotopes, of which 10 stable and 15 radioactive ones are known at present. The properties of the atom and of the atom-ions are discussed in detail. The formation of Sn_2 molecules on evaporation of tin from a Knudsen cell is of theoretical interest. 120 pages are devoted to the crystallographic, mechanical, thermal, electrical, magnetic, and optical properties, and 96 pages to the electrochemical behavior, which is of great practical importance for the plating industry and has accordingly been very thoroughly investigated. The last large chapters in the volume describe the chemical behavior of the metal and of its ions. Little space is taken up by a chapter on the physiological behavior of tin and its compounds, which would have been better headed "Toxicity" in accordance with the marginal notes in English, particularly since there is a section entitled "Antidotes". The data on methods of detection, determination, and separation in the last chapter are largely confined to a list of references to secondary literature. A table gives the most sensitive reactions of Sn.

The volume contains a number of linguistic shortcomings with regard to chemical terminology, *e.g.* the statement on p. 1 that: "Sn^{II} oxydiert leicht zu Sn^{IV}." Terms such as "unedles Normalpotential" (p. 397), "Ammoniumhydroxidlösung" (p. 365), and "sulfidierung" (p.354) also prove disturbing. It is incorrect to state that α-tin is known as tin plague (p. 130). On the contrary, tin plague is the conversion of white β-tin into gray α-tin, since "pimples" formed from gray tin at isolated points on white tin have an "infectious" action on the surrounding areas. In the section on the transition from β-tin into α-tin (p. 131) or in connection with the preparation of gray tin (p. 37), it is interesting to note that no reference is made to pink salt, $(NH_4)_2[SnCl_6]$, which is mentioned in all the textbooks as an accelerator of the transition.

The incorrect formula NH_4CNS has been copied from the original literature, instead of NH_4SCN, for ammonium thiocyanate (p. 51).

The literature has been evaluated up to the end of 1969, and more recent publications are also included in some cases.

Ekkehard Fluck [NB 89 IE]

Episome (Episomes). By *A. M. Campbell.* Moderne Biowissenschaften, Vol. 1. Akademie-Verlag, Berlin 1971, 1st Edit., 203 pp., numerous illustrations, bound, DM *ca.* 32.—.

A review of episomes and related topics (section headings: historical introduction, temperate bacteriophages, transfer agents, bacterial plasmids, and partial diploidy) is followed by a presentation of experimental results (mode of chromosomal attachment, mechanism of chromosomal attachment, mechanism of detachment, abnormal detachment, and the formation of transducing phages, immunity and its genetic control, autonomous replication, joining and separation of ends, polylysogeny). The book ends with a general examination of the definition of the episome and a chapter on episomes as model systems, in which an attempt is made to apply the results obtained with the episome-bacterial chromosome system to the situation prevailing in the case of eukaryotic chromosomes and to fit them in the general biological framework.

The particularly well known λ phage is used extensively as an example. The operative organization of the λ genome and the regulation mechanisms that allow integration of the phage genome into the bacterial genome can also serve as a model for regulation in higher cells. Tumor viruses, whose genomes are attached to the chromosomes of eukaryotic organisms [*H. M. Temin*, Sci. Amer. *226*, no. 1, p. 24 (1972)] and the possibility of curing genetically defective human cells *in vitro* with the aid of transducing phages [*C. R. Merril, M. R. Geier*, and *J. C. Petricciani*, Nature *233*, 398 (1971)] show that the episome concept described here is not restricted to bacteria. The attachment of viral chromosomes to bacterial chromosomes by simple exchange may be regarded as a model for the crossing-over in meiosis, but could also indicate a way in which an increase of DNA in eukaryotic chromosomes could have come about through evolution. The attachment of concatemeres formed in the replication of viral DNA could have contributed to the DNA redundancy so typical of the eukaryotes. In view of these many aspects, the readership of this book should not be restricted to those interested in microbial genetics.

The monograph was originally published in English by Harper & Row in 1969. Some recent findings have been incorporated by *E. Geissler*, the editor of the present series, in the form of footnotes and figures. This translation is most welcome, if often somewhat too literal.

Günter Obe [NB 90 IE]

Spectroscopy in Inorganic Chemistry. Vol. 1. Edited by *C. N. R. Rao* and *J. Ferraro.* Academic Press, New York—London 1970. 1st Edit., xii. 410 pp., numerous illustr., bound, $ 19.50.

A very wide variety of spectroscopic methods have in recent years found increasing importance in structural

investigations. This has led the editors to present a collection of articles designed to give the inorganic chemist an understanding of modern spectroscopic methods and to provide him with some ideas about the application of these methods to his own particular problems. In the light of this avowed aim, it is understandable that practically every one of the nine contributions begins with a detailed introduction to the experimental and theoretical principles of the methods. Descriptions of special applications follow, some of them selected from the individual authors' work. The treatment is not always comprehensive, which is scarcely surprising in view of the size of the book. One exception is the article by *Ballhausen* concerning the spectroscopy of ionic crystals, in which one problem encountered in this area is examined in a highly interesting manner. Many a chemist will find this article quite difficult reading.

The present work will be found useful by anyone wishing to acquaint himself with the principles and range of application of the methods discussed. The extensive literature cited provides the reader with easy access to the original work. The specialist in this field will not find much in the way of new information.

H.-G. Kuball [NB 91 IE]

Molecular Acoustics. By *A. J. Matheson.* John Wiley & Sons Ltd., New York—London 1971, 1st Edit., xvi, 290 pp., numerous figures and tables, bound £ 5.50.

Very detailed information on the interaction between molecules in the gas phase, in liquids, in solids, and in high polymers can be obtained from investigations on the propagation of high-frequency sound waves. In addition to questions of energy transfer in gases and liquids *Matheson*'s book deals especially with problems that are of interest to the chemist, such as the determination of energy barriers in molecules exhibiting internal rotation, as well as viscoelastic properties of dilute and concentrated solutions of polymers, including the rotational isomerization of polymers and the helix-coil transitions in polypeptides. The investigations in solution, such as the association of ions by ultrasonic waves, are also discussed. A short chapter is devoted to the propagation of sound waves in solids, including semiconductors and ferromagnetics, and the influence of dislocations on the damping of sound waves.

The author deals briefly with the experimental methods used for the measurement of the velocity, dispersion, and absorption of sound. The fundamental theoretical views are presented in an easily understandable manner.

The book can be particularly recommended to those who wish a general picture of the possibilities offered by the investigation of the propagation and absorption of sound for the treatment of various chemical problems.

H. Gg. Wagner [NB 92 IE]

Pulse and Fourier Transform NMR. Introduction to Theory and Methods. By *T. C. Farrar* and *E. D. Becker.* Academic Press, New York—London 1971. 1st Edit., 115 pp., bound $ 7.50.

Two basic recording techniques are now available to the NMR spectroscopist. One is the normal continuous scanning of the Larmor frequency range of a nucleus, *i.e.* continuous wave (CW) NMR spectroscopy, and the other is the simultaneous excitation of all the Larmor frequencies of a nucleus with strong radio-frequency pulses of short duration, followed by Fourier transformations of the resulting time-dependent free induction signal, *i.e.* pulse Fourier transform (PFT) NMR spectroscopy. The PFT method is faster and more sensitive than the CW technique. These advantages, supported by the development of commercially available PFT-NMR spectrometers, have helped to open up PFT-NMR spectroscopy. The present monograph takes this into account and fills a gap in the introductory NMR literature.

Fundamental concepts such as nuclear energy states, relaxation, nuclear precession, and free induction are explained accurately and concisely. Vector calculation is briefly reviewed to allow a better understanding of nuclear magnetic processes. Two sections dealing mainly with equipment present an outline of instrumental requirements regarding the spectrometer, pulse unit, and computer. The authors describe relaxation mechanisms and refocusing and spin echo methods for the measurement of relaxation times. They thus stress the growing importance of relaxation times as structural parameters alongside chemical shifts and coupling constants. Topics touched upon in two special sections include nuclear nutation and spin echo experiments as well as possibilities for the use of the pulse technique to follow diffusion, exchange, and molecular dynamic processes.

102 sources are cited for further reading on methods. The absence of a section on pulsed homonuclear and heteronuclear double resonance, which can now be carried out as a routine method, is hardly surprising in view of the planned restriction of the book to about 100 pages, particularly since introductory monographs on nuclear magnetic double resonance already exist. The book is systematically organized and clearly and skillfully written, and should therefore present no difficulty even to the less experienced reader.

Eberhard Breitmaier [NB 93 IE]

Stereochemistry of Carbohydrates. By *J. F. Stoddart.* Wiley-Interscience, New York 1971. 1st Edit., xi, 249 pp., numerous illustrations, bound, £ 7.00.

This is a splendid book, and one for which we have been waiting a long time. It should find general acclaim not only among carbohydrate chemists but also among all those interested in questions of stereochemistry. Carbohydrate chemistry has contributed a great deal—for instance in the field of conformational analysis—that is important for all chemists working in organic chemistry and biochemistry, and it is therefore most pleasing that a systematic review of this field has at last appeared. Most chemists are unaware of the wealth of material in the form of excellent model substances that carbohydrate chemistry has to offer for the study of stereochemical and mechanistic problems. The present book should considerably facilitate access to material that can sometimes be quite tricky. For example, it is worth recalling that the problem of the anomeric effect was discussed for years among carbohydrate chemists before it became familiar to all chemists as a phenomenon generally encountered in heterocycles.

The book provides a clear survey of all the most important aspects of stereochemistry. It is divided into five chapters, an introduction being followed by a discussion of the problems of constitution and configuration, conformation, physical methods, and isomerism. The book is written in

an up-to-date manner, and every effort has been made to include the most recent results. In the circumstances, one is quite prepared to make due allowance for the odd shortcoming, brought about by the fact that one or two of the chapters were written in some haste. The new nomenclature on conformations of five- and six-membered rings in monosaccharides agreed by the British-American commissions has been used, although it has not yet been published by the IUPAC commissions. The nomenclature is simple and should help to clear up some of the confusion that has prevailed hitherto, so that it is likely to become accepted. The book may be warmly commended to carbohydrate chemists and to all those with an interest in stereochemistry.

Hans Paulsen [NB 94 IE]

Physicochemical Characteristics of Oligonucleotides and Polynucleotides. By *B. Janik*. IFI-Plenum, New York—Washington 1971. 1st Edit., vii, 213 pp., bound $ 20.—.

The title of the book is inviting, as there has been no comprehensive treatise on the physical and chemical properties of this group of substances since "Polynucleotides" by *Steiner* and *Beer*, published in 1961. However, one soon also begins to doubt whether this is possible in about 200 pages, since *Michelson* in 1963 was hard put to give even a sketchy picture of the material from 421 sources in the corresponding chapter of his book. What can one and what should one expect, therefore, from such a bold title?

It conceals a tabulated collection of data and literature in three chapters embracing the following topics: dissociation properties, spectral data, melting points. This is undoubtedly a selection of a few important physico-chemical properties of oligonucleotides and polynucleotides. However, one quickly becomes reconciled to this limitation, since the book proves to be a very handy collection of data because it is well classified and complete, and its recent data gives it an additional advantage over *Sober*'s 1968 "Handbook of Biochemistry".

The tabulated part is preceded by a chapter on its use. This chapter should be read carefully, since very extensive use has been made of symbols and abbreviations in classifying the material, *e.g.* to indicate data that were not taken directly from a publication, but were read from its diagrams.

Each chapter is preceded by a short text with definitions and special explanations to allow direct comprehension of the succeeding tables. Footnotes are also used to describe complicated situations. This arrangement allows a rapid and accurate grasp of the contents of the tables, which can be checked and if necessary expanded with the aid of the appended references. The arrangement of the tables can be illustrated by the chapter on dissociation properties, in which the material is grouped in the following columns: name of substance, measuring method, measuring temperature, medium, pK_{mono}, pK_{poly}, notes, references. *Janik* bases his book on a total of 289 references extending up to the end of 1970.

The book can be wholeheartedly recommended to anyone working in this field, since it offers a great deal of information, and hence saves work, at a reasonable price. Since it will quickly lose its up-to-date character with the passage of time, however, it is advisable to buy it soon!

Alfred Maelicke [NB 95 IE]

Fast Reactions. By *D. N. Hague*. John Wiley & Sons, New York—London 1971. 1st Edit., viii, 159 pp., numerous figures, bound £ 3 —.

The book is divided into four chapters, which are followed by four short appendixes. The first chapter deals briefly with molecular beam experiments and also presents a very short discussion of the diffusion-controlled reaction. The second chapter, on experimental methods, forms the heart of the book, both in its subject and in its size. Despite the need to deal with very diverse measuring methods in a fairly limited space, this chapter provides a good survey of the methods that have been used so far in the kinetics of fast reactions.

The last two chapters are concerned with selected results from the extensive literature on fast chemical reactions. The third chapter concentrates mainly on elementary processes (reactions of protons, electrons, and metal ions), while the examples in the fourth chapter are taken from reactions that are of biological interest (enzymes, nucleic acids). However, the section on metal complex formation could have been more comprehensive. It should also be noted that an error has crept into the discussion of the log k/pK relation in the last chapter: the slope factor α should not appear in the exponent when the equation is written in the logarithmic form.

The exercises appended to each chapter underline that this book is intended for students.

On the whole it provides a lucid introduction to the field of fast chemical reactions. It can be recommended to all students and newcomers to reaction kinetics as a primer, and to the more advanced as a useful addition to the existing literature.

Marie-Luise Ahrens [NB 96 IE]

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Displacement Reactions of Phosphorus(V) Compounds and Their Pentacoordinate Intermediates[1]

Paul Gillespie, Fausto Ramirez, Ivar Ugi, and Dieter Marquarding[*]

Reactions of phosphorus(V) compounds involving the mutual interconversion of tetra- and pentacoordinate species are discussed in a critical review emphasizing stereochemical implications of the reaction mechanism. This discussion includes the formation and decomposition of the stable oxyphosphoranes, the Michaelis-Arbusov, Perkov, and Wittig reactions, interconversions of phosphines and their oxides, and the nucleophilic displacements on phosphonium compounds. Reactions of phosphate esters and related compounds receive particular attention. All chemical arguments are derived by considering the effect of factors determining the relative stabilities of phosphorane derivatives, their rates of formation, decomposition and rearrangement by bond deformation or rupture and recombination processes, considerations which are uniformly applied on the basis of concepts developed in a preceding communication[2]. It is shown that a comprehensive mechanistic interpretation of the foregoing reactions requires substantial addition to available conceptual foundations such that, in many cases, present concepts and mechanisms must be revised.

1. Introduction

Interest in the interconversions of tetracoordinate phosphorus compounds pervades many fields of pure and applied organic and inorganic chemistry including biochemistry. Much of this interest is due to the fact that certain phosphoric acid derivatives are essential to life processes in a great variety of ways while others inhibit some vital reactions.

The voluminous literature on the mechanistic aspects of tetracoordinate phosphorus chemistry[3–18] gives the impression that most of the fundamental problems in this field have been solved with only peripheral questions left unanswered. This review critically examines which of the published conclusions are firmly justified by the existing evidence and what additional statements can safely be made.

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[**] In this paper the following abbreviations are used:
ADP = adenosine diphosphate
AMP = adenosine monophosphate
ATP = adenosine triphosphate
BPR = Berry pseudorotation [2,38]
BE = binding energy
TBP = trigonal bipyramid(al)
TR = turnstile rotation [2,29,46]

A consistent treatment of the mechanistic problems in this field requires extension and revision of mechanistic concepts in prior use. Reactions under consideration in this review are discussed in terms of the properties of the pentacoordinate intermediates that are involved. The mutual interconversions of tetra- and pentacoordinate phosphorus compounds are interpreted by invoking facial attack of nucleophiles upon tetracoordinate species, in some cases followed by permutational isomerization of the pentacoordinate adduct, with attendant apical departure of a leaving group from the phosphorane derivative.

The various factors that determine the respective stabilities of the permutational isomers of the pentacoordinate intermediates are also discussed on the basis of concepts developed in a preceding communication[2].

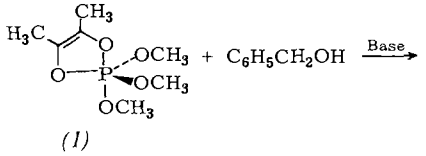
2. Some Properties of Oxyphosphorane Derivatives

The existence of stable oxyphosphoranes[19,20] provides a sound basis for the hypothesis that metastable oxyphosphoranes are intermediates in many reactions of phosphorus(v) compounds.

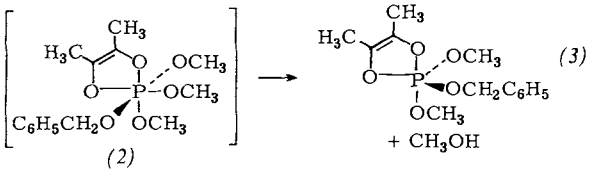
Isolable phosphorane derivatives are generally capable of rapid reorganization by bond-deformation processes, *i.e.*, "regular" permutational isomerizations.

The base catalyzed exchange of alkoxy groups that is observed when oxyphosphoranes are treated with alcohols[21] clearly shows that these systems are capable of undergoing reactions *via* hexacoordinate species (see Reaction 2.1). It follows that an analogous substitution process, involving the alcohol which corresponds to one of the alkoxy groups on the phosphorane, may result in an irregular permutational isomerization of the latter[2].

Reaction 2.1[21]



(1)



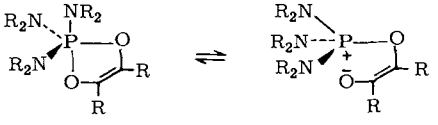
(2) *(3)*

The exchange of alkoxy groups in *(1)* proceeds with ring retention and is strongly catalyzed by 2,4,6-trimethylpyridine. It is reasonable to assume that this reaction involves the addition and subsequent elimination of alkoxy groups *via (2)*, which may be either a transition state or an intermediate. In this context, the base catalyzed hydrolysis of halogeno-amine-cobalt complexes should be mentioned; these are said to occur by the addition of water to a trigonal bipyramidal pentacoordinate cobalt complex[22].

The dissociation of phosphoranes into pairs of ions is supported by experimental evidence[23–25]. This or other related phenomena[26,27] can cause the irregular permutational isomerization of certain phosphoranes.

The rearrangement of phosphoranes *via* tetracoordinated intermediates is observed when electron donating groups stabilize the phosphonium ion and when one of the phosphorane ligands is a good leaving group. Compound *(4)* in Reaction 2.2 exists[25a,b] in two crystalline forms, the phosphorane derivative *(4a)* and the zwitterion *(4b)*. NMR data indicate that, in solution, both isomers yield the same fast equilibrium system, whose composition is solvent dependent. The ^{31}P chemical shift of *(4)* results from the chemical shifts of the phosphorane ($\delta^{31}P = +40$ ppm *vs.* H_3PO_4) and phosphonium ($\delta^{31}P = -40$ ppm *vs.* H_3PO_4) nuclei[25a,b].

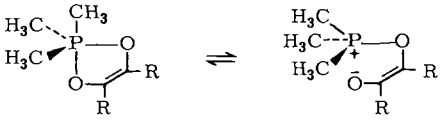
Reaction 2.2[25a,b]



(4a) *(4b)*

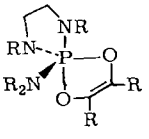
Analogous equilibria are also observed among trialkyldioxyphosphoranes[25c,d], *e.g. (5a)* ⇄ *(5b)* (cf. Reaction 2.3).

Reaction 2.3[25c,d]



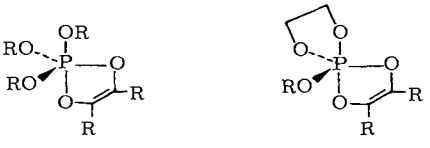
(5a) *(5b)*

Spirophosphoranes show a greater tendency to exist in the pentacoordinate state than the corresponding monocyclic systems, and only the phosphorane form of *(6)* can be observed [compare with *(4a)* ⇄ *(4b)*][25a,b].



(6)

Relatively high ligand electronegativity[28] favors the phosphorane *vs.* the phosphonium structure, and among compounds with five oxygen ligands, only the phosphorane structures *(7)* and *(8)* are observed in both monocyclic and spiro derivatives[25a,b].

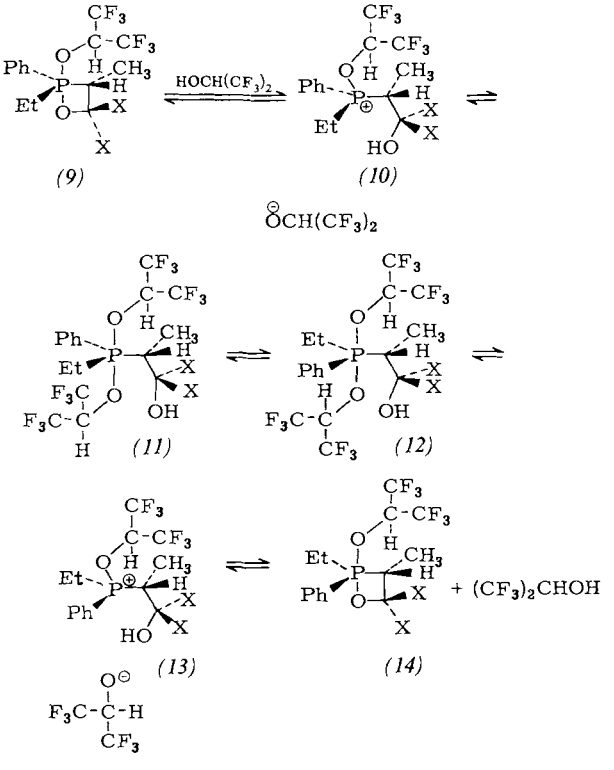


(7) *(8)*

Recently, examples of acid catalyzed irregular permutational isomerizations[2,29,30] *via* tetracoordinate intermediates have been observed. The two four-membered ring oxyphosphoranes[31] *(9)* and *(14)* are epimers which differ with respect to the configuration of the TBP center of chirality. The ^{31}P-NMR resonance of *(9)* appears at $\delta^{31}P = +30.3$ ppm, that of *(14)* at $\delta^{31}P = +21.0$ ppm. The interconversion of *(9)* and *(14)* by regular processes in neutral aprotic media is not possible because the necessary sequences of BPR or TR processes would involve species with prohibitively high energies, *e.g.*, with a diequatorial four-membered ring and apical P—C bonds[19d,31]. (The reader is referred to the footnote [**] at the beginning of this article for an explanation of the abbreviations used here and in the following text.)

The isomerization *(9)* ⇄ *(14)* is observed only in the presence of an acidic catalyst such as hexafluoroisopropyl alcohol; in the absence of the catalyst, no isomerization takes place[29]. Rapid hydrolysis of *(9)* and *(14)* occurs with formation of the acidic hexafluoroisopropyl alcohol; therefore, to avoid interconversion of *(9)* and *(14)*, moisture must be rigorously excluded. The mechanism shown in Reaction 2.4 accounts for these observations.

Reaction 2.4[29a]



The discovery of this type of *acid catalyzed irregular permutational isomerization*[29,30] emphasizes the necessity of determining the regular or irregular nature of a given process before attempting to provide mechanistic interpretations of it. The Selection Rules[5,8c-e] for phosphate ester hydrolysis do not account for this aspect of the problem and should therefore be carefully reexamined.

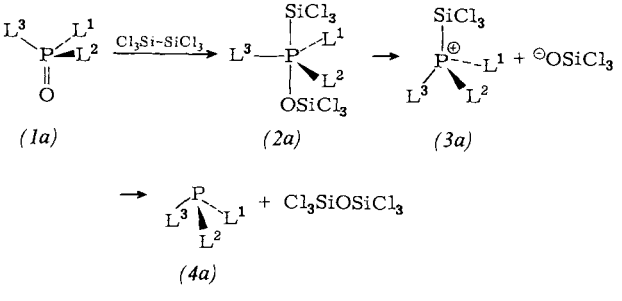
Some of the most revealing information on phosphorane derivatives has emerged from X-ray crystallographic analyses of four-membered[31b,c] and five-membered[32,33] cyclic oxyphosphoranes. The apical bonds in the TBP are longer than the corresponding equatorial bonds. The skeletal placement of the four-membered ring, as well as that of the five-membered ring, is apical-equatorial. *There is a great deal of intramolecular crowding in TBP phosphoranes*, some distances between non-bonded atoms are as short as 2.63 Å. One of the consequences of this phosphorane structural feature is that their stability is markedly increased by the presence of four- and five-membered rings. The decrease in intramolecular crowding in the TBP can outweigh the ring strain resulting on deformation of bond angles within the rings. On the other hand, ring strain rather than intramolecular crowding is the main factor in determining the stability of tetracoordinate phosphorus. This basic difference between phosphorus in its two coordination states has an important consequence for the chemistry and biochemistry of phosphate esters. Relative to the corresponding compounds in which the phosphorus is not incorporated in rings, a five-membered cyclic phosphate ester loses in stability, while the corresponding cyclic phosphorane gains in stability. Hence, there is thermodynamic and kinetic advantage in adding a nucleophile such as hydroxide or alkoxide to tetracoordinate phosphorus to form a phosphorane intermediate when a five-membered ring is present in the phosphate, or when this ring is easily formed during a reaction, in particular, if this process is rate determining[19d]. This important theme will recur often throughout this Review.

3. Steric Course of the Reduction of Phosphane Oxides and of Displacement Reactions of Phosphonium Compounds and Related Reactions

3.1. Acyclic Systems

The reduction of optically active *acyclic* phosphane oxides *(1a)* with silane derivatives (excepting trichlorosilane[34]) proceeds with inversion of configuration at the central phosphorus atom[3,13]. A plausible mechanism[3] for this reaction is shown in Reaction 3.1. Accordingly, the reduction of phosphane oxides is closely related to the displacement reactions of the phosphonium compounds.

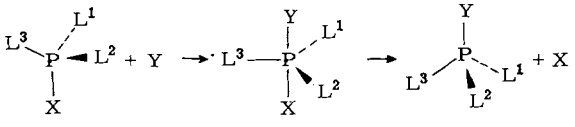
Reaction 3.1



These reactions correspond to the general pattern of Reaction 3.2, whose essential features were established *ca.* 40 years ago by *Ingold et al.*[35a,b] and formulated for the first time explicitly with an intermediate of type *(2)* by *McEwen et al.*[35c-g].

The stereochemical pattern of Reaction 3.2 applies generally to the reduction of acyclic phosphinates[36, 37] which resemble the phosphane oxides[3] and to the displacement reactions of acyclic phosphonium ions[4, 35] when the nucleophile Y attacks the tetrahedron at the face opposite the leaving group X. If this is the case, the leaving group X will appear in an apical position of the TBP intermediate *(2)*. The TBP *(2)* with apical X is favored by the "polarity rule"[2, 38–40] when X is significantly more electronegative than the ligands L^1, L^2, and L^3. The polarity rule[39,40], a semiempirical rule based upon experimental observations and theoretical deductions, will be discussed in Section 4.3. In most "normal" reactions of the type under consideration, X is substantially more electronegative[28] than L^1, L^2, L^3, and the stereochemical pattern of Reaction 3.2 is indeed observed. However, if X, L^1, L^2, and L^3 do not differ significantly in electronegativity, a different stereochemical pattern may be observed for the reaction.

Reaction 3.2



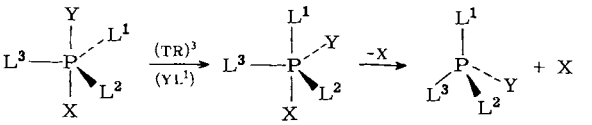
(1) *(2)* *(3)*

Any constraint that prevents the leaving group X from becoming apical, or that forces one of the ligands L^1, L^2, or L^3 to become apical while the TBP intermediate is being formed will also result in a steric course different from that of Reaction 3.2. The most important of these constraints[2,19d] originates with the presence of four- or five-membered rings. This feature forces one of the ligands that forms part of the ring into an apical position in the TBP, with consequences that will be discussed in Section 3.2. In general, nucleophiles attack the faces of skeletal tetrahedra and appear in the apical position of the TBP pentacoordinate species[2–5, 41–45]. When the tetracoordinate atom is phosphorus and the pentacoordinate TBP species is an intermediate, the next step is the decomposition of the intermediate by departure of the leaving group X from the apex of the TBP. Apical departure of X from *(2)* [without any permutational isomerization of *(2)*] gives the tetracoordinate species *(3)* which is heterochiral[30] to *(1)* if the entering and leaving groups are considered to be equivalent, *i.e.*, the displacement proceeds with inversion[3,4c,35c–e,g,36,37]. [Likewise, *(4a)* in Reaction 3.1 can be regarded as heterochiral to *(1a)*.]

A displacement of X by Y in tetrahedron *(1)* will occur with retention of configuration when the product is the optical antipode *($\bar{3}$)* of *(3)*, since *($\bar{3}$)* is homochiral[30] to *(1)* (Reaction 3.3).

The displacement with retention *(1)*→*($\bar{3}$)* *via* the TBP *(2)* requires the permutational isomerization of the latter by a triple or $(TR)^3$ process[2,29,46], or by a sequence of three single TR processes or of three BPR. One TR or BPR, or an even number of them, cannot result in displacement with retention. One of the $(TR)^3$ processes which exchange Y and a ligand L, without affecting X and the other two ligands L, is depicted in Reaction 3.3. In this illustration, Y and L^1 exchange positions to give TBP *(5)*, from which apical departure of X results in tetrahedron *($\bar{3}$)*, homochiral to *(1)* (retention).

Reaction 3.3



(2) *(5)* *($\bar{3}$)*

As a rule, the nucleophile Y (as well as the leaving group X) is more electronegative (*i.e.*, more apicophilic; see Section 4.3) than L^1, L^2, or L^3. Consequently, TBP *(2)* (which leads to inversion without permutational isomerization) is energetically favored over TBP *(5)* (which could lead to retention) by the polarity rule. All these effects then favor the pattern of Reaction 3.2, *i.e.*, displacement with inversion for acyclic systems where X and Y are more apicophilic than L^1, L^2, and L^3.

Consider now the case in which X and the ligands L^1, L^2, and L^3 do not differ substantially in apicophilicity. The situation becomes more complex, but not, we believe, for the reasons given in the previous literature[3]. As X, L^1, L^2, and L^3 become comparable in apicophilicity, the preference for the attack by the nucleophile Y at the tetrahedral face opposite X vanishes. Attack by Y on the remaining three faces opposite to L^1, L^2, and L^3, respectively, can place these ligands in an apical position of a TBP, to the extent that this is allowed by the electronegativity and the steric requirements of these ligands (the apical positions are subject to more steric hindrance than the equatorial positions). Now, the intermediate TBP can decompose by the reverse process, or can undergo certain permutational isomerizations that will bring X to the apical position from which it can then depart; cf. Reaction 3.4.

The mechanisms by which regular permutational isomerizations of TBP take place have been discussed in detail[2,29]. Here we need only summarize the conditions necessary to observe displacements with inversion or retention of tetrahedral configuration by the TR and the BPR processes, when the nucleophile Y must enter at the face opposite the leaving group X, and when Y can enter at any one of the four faces of the tetrahedron, *i.e.*, opposite L^1, L^2, L^3, or X.

If Y must enter at the face opposite X, *inversion* can result without any TR or BPR, or after $(TR)^2$, or after a sequence of an even number of single TR or BPR[46]. Retention can occur only after $(TR)^3$, or after a sequence of three single TR or BPR. Retention cannot be the result of one single TR or one BPR, because in those cases the leaving group X is transferred to an equatorial position from which it cannot depart to form a tetrahedral arrangement.

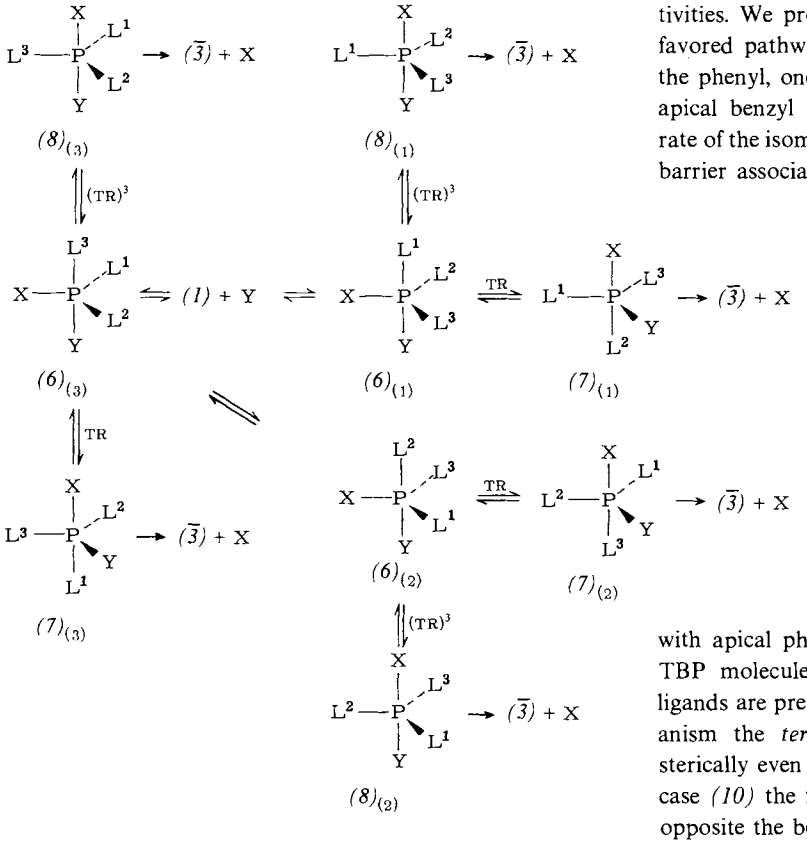
If Y can enter at the faces opposite L^1, L^2, or L^3, *inversion* can occur only after $(TR)^2$, or after a sequence of an even number of single TR or BPR. *Retention* can occur after one single TR or one BPR, (assuming that Y is able to move to an equatorial position as a result of that isomerization) or a $(TR)^3$, (see Reaction 3.4).

Table 1. Summary of the steric course of substitution reactions of tetracoordinate phosphorus compounds *via* oxyphosphoranes.

Position of entry of Y	Permutational isomerization of the TBP intermediates	Stereochemical result at the P-center
opposite X	none	inversion
opposite X	one BPR or one TR	no reaction
opposite X	two BPR or two TR or one $(TR)^2$	inversion
opposite X	three BPR or three TR or one $(TR)^3$	retention
opposite L^1, L^2, or L^3	none	no reaction
opposite L^1, L^2, or L^3	one BPR or one TR	retention[a]
opposite L^1, L^2, or L^3	two BPR or two TR or one $(TR)^2$	inversion
opposite L^1, L^2, or L^3	three BPR or three TR or one $(TR)^3$	retention

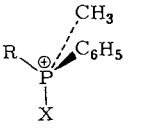
[a] Assuming that Y is able to move to an equatorial position.

Reaction 3.4



With these considerations in mind, it should be clear from Reaction 3.4 that the displacement will proceed with retention when the single TR or BPR can bring X to an apical position, *i.e.*, when the isomerization rearranges *(6)* in such a way that *(3)* is produced by the apical departure of X. On the other hand, displacement with inversion is possible only after those $(TR)^2$, or the corresponding sequences of two TR or BPR, capable of transforming TBP *(6)* into TBP *(2)* have occurred.

These concepts account for the observation that the phosphonium ion *(9a)* undergoes displacement of X by HO^- with retention[47] (Reaction 3.4), while the analogous ion *(9b)*[48], with one alkoxy ligand, undergoes displacement with inversion[48-50] (Reaction 3.2). Note that in *(9a)*, L^1, L^2, L^3, and X are of comparable electronegativities ($X = CH_2C_6H_5$), and Y can attack at the face opposite L^1 ($L^1 = C_6H_5$). In *(9b)*, L^1, L^2, and L^3 are of substantially lower electronegativity than X ($X = OC_2H_5$), and Y must attack at the face opposite it.



(9a), R = $C(CH_3)_3$, X = $CH_2C_6H_5$
(9b), R = $C(CH_3)_3$, X = OC_2H_5
(10), R = C_2H_5, X = $CH_2C_6H_5$

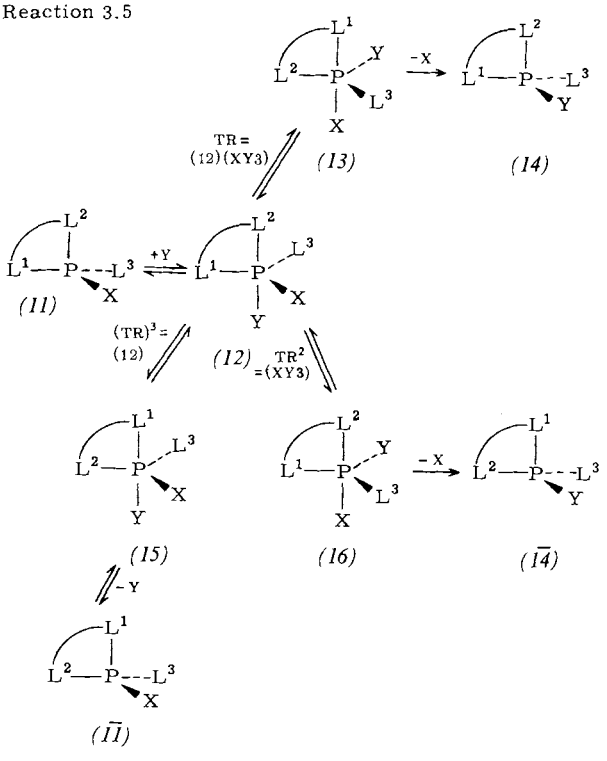
The phosphonium ion *(9a)* differs from *(10)* only in the size of one of the ligands, $(CH_3)_3C > C_2H_5$, and yet the former *(9a)* undergoes displacement with retention[47] and the latter *(10)* with inversion[4c,35c-g]. Both are examples of comparable X, L^1, L^2, and L^3 electronegativities. We propose that in the *tert*-butyl case *(9a)* the favored pathway is the attack of Y at the face opposite the phenyl, one rapid single TR or BPR, and the loss of apical benzyl (X); (retention by Reaction 3.4). The fast rate of the isomerization could be due to a very low energy barrier associated in part with the highly energetic TBP with apical phenyl and equatorial *tert*-butyl group. The TBP molecule is very crowded when relatively bulky ligands are present[19d,32,33] (see Section 4). In this mechanism the *tert*-butyl group need never move to the sterically even less favorable apical position. In the ethyl case *(10)* the favored pathway is attack of Y at the face opposite the benzyl, no permutational isomerization, and the loss of apical benzyl[4c,35c-g] (inversion by Reaction 3.2). In this case, the barrier for the TR or BPR required in the alternate pathway for retention is relatively higher.

3.2. Cyclic Systems

When the phosphorus atom of phosphane oxides and of phosphonium ions is incorporated into a small ring, *i.e.*, a four- or five-membered ring, the reduction and displacement reactions proceed, as a rule, with retention of the configuration at the reactive center[51-54] (see also ref.[55-57]), in contrast to the analogous reactions of *acyclic* systems where inversion is the normal stereochemical pattern (cf. Reaction 3.2). The reasons for this difference between four- and five-membered *cyclic* systems, on the one hand, and *acyclic* systems on the other hand, are

easily understood in terms of the TR mechanism[2,46]. Both the TR and the BPR processes are acceptable mechanistic alternatives to explain the permutational isomerizations of *acyclic* TBP phosphoranes. In four- and five-membered *cyclic* phosphoranes, the ring must always play the role of the "pair" in the single TR and the multiple $(TR)^n$ processes, and the remaining three ligands the role of the "trio". This provides the only general and consistent interpretation of the experimental data[2,29], and presumably results from the circumstance[2] that the lowest barrier for the TR is obtained when the pair angle is slightly smaller than 90°, while the trio angles are slightly larger than 90°. The analysis takes the following form in the situation under discussion[58]. Four- and, as a rule, five-membered rings are unable, for reasons of strain, to occupy the diequatorial position of a TBP molecular skeleton and must occupy the apical-equatorial position, even if this results in violation of the polarity rule. Consequently, the nucleophile Y must attack the skeletal tetrahedral face opposite one of the ligands that form part of the small ring in the cyclic tetracoordinate phosphorus compound, see *(11)*→*(12)*, and *(11̄)*→*(15)* in Reaction 3.5.

Reaction 3.5



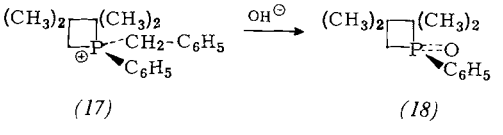
(11) *(12)* *(13)* *(14)* *(15)* *(16)* *(11̄)* *(14̄)*

Since the nucleophile Y must enter apically and one of the ring-ligands must also be apical, the leaving group X must always be equatorial; thus there must be permutational isomerization of TBP *(12)* for displacement of X by Y, if X must depart from the apical position. The cyclic TBP intermediate *(12)* is capable of undergoing a single TR, a $(TR)^2$ or a $(TR)^3$ process[46], and in general $(TR)^2$ and $(TR)^3$ processes tend to have higher barriers than the single TR process. The TR which uses the ring as the pair and which moves the leaving group X to an apical position is denoted by the permutation (1 2)(X Y 3) and transforms TBP *(12)* into *(13)*. Apical departure of X from *(13)* yields the tetrahedron *(14)* which is homochiral to *(11)* (retention).

The $(TR)^2$ which, again, uses the ring as the pair and moves X to an apical position is denoted by the permutation[2,29,30] (X Y 3)=$(TR)^2$ and transforms TBP *(12)* into *(16)*; apical departure of X from *(16)* yields *(14̄)*, the optical antipode of *(14)* and heterochiral to *(11)* (inversion). Since (TR) has, in general, a lower barrier than $(TR)^2$, retention of configuration, *(11)*→*(12)*→*(13)*→*(14)*, is the expected stereochemical pattern in cyclic tetracoordinate phosphorus compounds with small rings. Note the stereochemical consequence imposed by the ring in this case. Due to the fact that the nucleophile must enter opposite an apical ring ligand and that the ring must be the "pair", a $(TR)^3$ can only lead to inversion with no substitution, in contrast to the case for acyclic phosphoranes[2,29]. Interconversion of diastereoisomers by inversion at phosphorus in the *cyclic* system is due, in this interpretation, to the apical entry and departure of the nucleophile Y, to the occurrence of one $(TR)^3$, and to the need to involve the ring as the pair in the TR process[2,29].

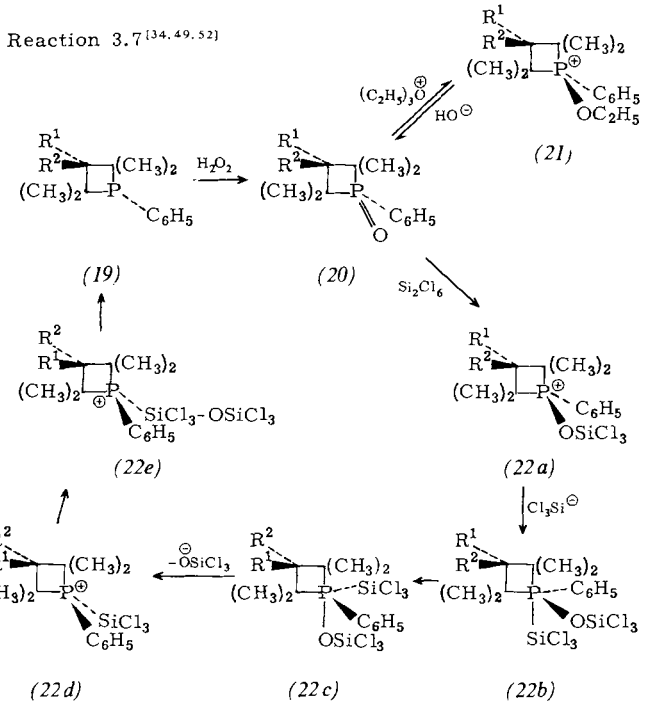
Reactions 3.6, 3.7, 3.8, and 3.9 are reported examples in which phosphonium compounds and phosphane oxides containing small rings undergo displacements and reductions, respectively, with retention of the phosphorus configuration. (In Reaction 3.7, the displacement is *(21)*→*(20)*, and the reduction is *(20)*→*(22)*→*(19)*.)

Reaction 3.6[51]



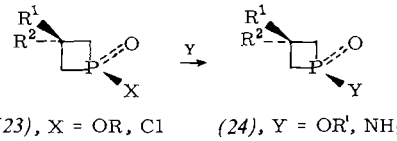
(17) *(18)*

Reaction 3.7[34,49,52]



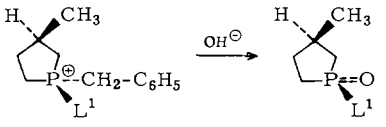
(21) *(19)* *(20)* *(22e)* *(22a)* *(22d)* *(22c)* *(22b)*

Reaction 3.8[53]



(23), X = OR, Cl *(24)*, Y = OR', NH_2

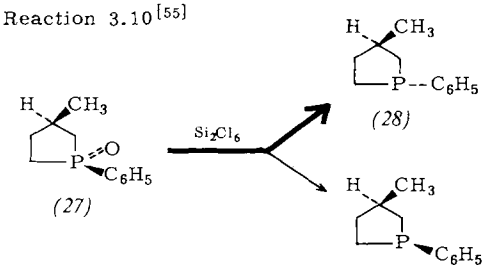
Reaction 3.9 [54, 57]



(25a), $L^1 = CH_3$ (26)
(25b), $L^1 = C_6H_5$

Reaction 3.10 describes some observations that have defied interpretation in the past[55]. The reduction of the cyclic phosphane oxide (27) proceeds to give predominantly (28) with inversion, rather than (29) with the expected retention: [(28)] ≫ [(29)].

Reaction 3.10 [55]

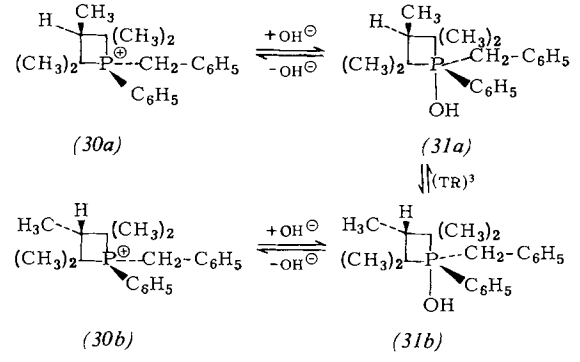


(27) (28) (29)

This anomaly can be explained in one of two ways. In the first, (28) and (29) are formed according to the pattern of Reaction 3.5, but in this case the barrier for $(TR)^2$ must be lower than that for the single TR, hence (12) ⇄ (16) ⇄ (14) is favored over (12) ⇄ (13) ⇄ (14), and inversion results[58]. A second interpretation is that the homochiral product is formed according to Reaction 3.5: (11) ⇄ (12) ⇄ (13) ⇄ (14), or (27) → (29), while the heterochiral product (inversion) is formed according to Reaction 3.1: (1a) → (2a) → (3a) → (4a), or (27) → (28). In this interpretation, the TBP intermediate (2a) must have a diequatorial five-membered ring, but the high strain associated with this situation[2] (*ca.* 40 kcal/mol) could certainly be offset by the placement of the relatively apicophilic ligand X = $OSiCl_3$ in apical position in (2a), but in equatorial position in (12); likewise the carbon = L^2 is equatorial in (2a) but apical in (12). Therefore, TBP (2a) may be favored over (12) by the effect of the modified polarity rule *vs.* ring strain, in this particular case.

Reaction 3.11 is an illustration of inversion of configuration at the phosphorus center of chirality without any substitution of one group by another. In our interpretation, the pathway is (11) ⇄ (12) ⇄ (15) ⇄ (11), of Reaction 3.5, where there is a $(TR)^3$ process with the small ring forming the pair and the other ligands the trio. This is favored because it brings back the most electronegative ligand OH to the apical position (31a) → (31b)[2].

Reaction 3.11 [3,56]

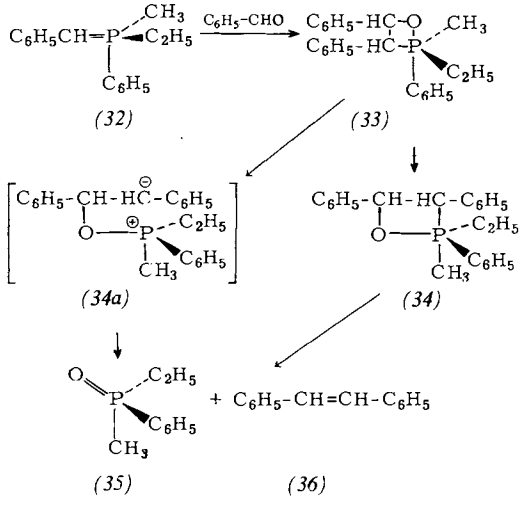


(30a) (31a) (30b) (31b)

Reaction 3.12 represents the application of these concepts to the interpretation of the retention of configuration about phosphorus during a Wittig olefin synthesis[4c, 30, 35d, f, g].

The interpretation of the Wittig reaction by invoking one or more pentacoordinate intermediates and employing the apical entry and departure concept for the formation and decomposition of the TBP requires one to force the first pentacoordinate adduct (33) to form either (34) or (34a). It is conceivable that the decomposition of (33) to products (35) and (36) is concerted with reorganization (*i.e.*, by a TR process) such that the breaking C—O and P—C bonds are already weakened in the TR barrier situation. The fact that the ring must be the pair in the TR forces retention on the reaction (see also ref.[29]).

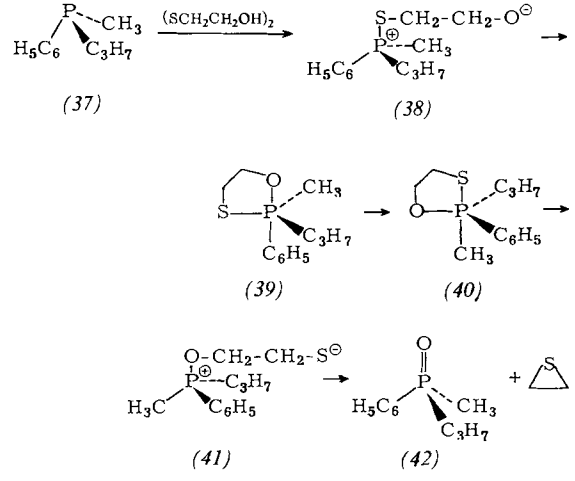
Reaction 3.12 [35d, g]



(32) (33) (34a) (34) (35) (36)

The steric course of Reaction 3.13 is an obvious consequence of apical entry and departure and a TR process with the ring as the pair.

Reaction 3.13 [13b]



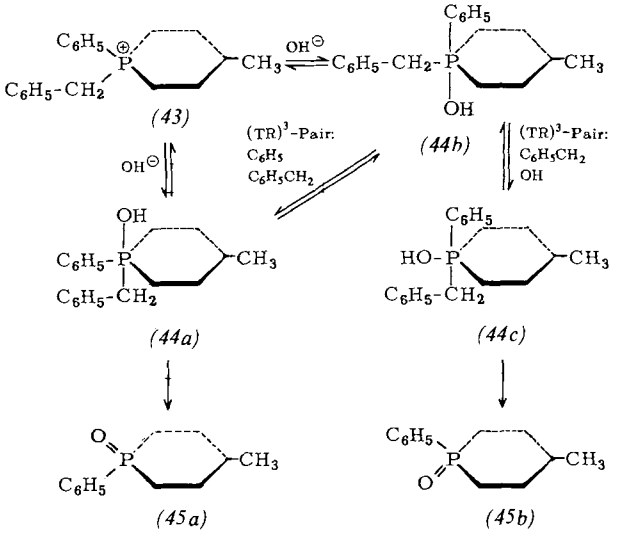
(37) (38) (39) (40) (41) (42)

Six-membered and larger rings are free of the constraints to which the small rings are subject. In general, if apicophilicity considerations so allow, the six-membered rings prefer the diequatorial placement, but can also adopt an apico-equatorial attachment. If the six-membered ring occupies the preferred diequatorial arrangement, then it functions as part of the trio in the TR processes, and in such a case, TR and $(TR)^2$ will move it into an apico-equatorial attachment, *while $(TR)^3$ will leave it diequatorial.* It should be noted that with a diequatorial six-membered ring, if one insists on invoking the BPR process, one must use a ring member as a pivot which leads to an apico-equatorial ring placement; otherwise, the ring would have to span the two apical positions of the new TBP skeletal arrangement.

If the six-membered ring occupies the apico-equatorial placement, and it functions as the pair of TR processes, then TR, $(TR)^2$, and $(TR)^3$ will necessarily leave it in the apico-equatorial placement, although the ring termini will exchange the skeletal positions as a result of TR and $(TR)^3$, but not $(TR)^2$. The participation of the ring in the trio of the TR or $(TR)^2$ can result in apico-equatorial placement with exchange of termini, or in diequatorial placement of the ring, while in the $(TR)^3$ the ring retains its placement.

In the six-membered cyclic systems, just as in the acyclic case, displacements occur normally with inversion (Reaction 3.2). An apparent exception is illustrated in Reaction 3.14 where there is some retention[57], although inversion is preferred. If one assumes here the preferred diequatorial placement and keeps the ring in that attachment, then the results can be interpreted in terms of nucleophilic displacement involving a $(TR)^3$ reorganization of the TBP intermediate *(44)*, using the ring as part of the trio. Note that in Reaction 3.14 there is not much difference in the electro-

Reaction 3.14[57]

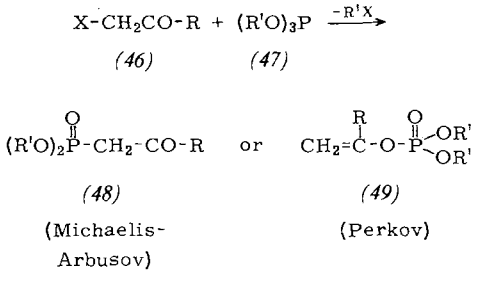


negativities of the leaving group X and of the ligands L^1, L^2, and L^3. Here, the preference is for apical phenyl (L^1), as in TBP *(44b)*, rather than apical benzyl (X) as in TBP *(44a)*. However, retention requires a $(TR)^3$, *(44b)* → *(44c)* → *(45b)*, while inversion requires no permutational isomerization, *(44a)* → *(45a)*.

3.3. A Note on the Perkov and the Michaelis-Arbusov Reactions

The reactions of trivalent phosphorus compounds with α-halocarbonyl compounds (Reaction 3.15) provide one of the most intriguing and controversial mechanistic problems in phosphorus chemistry[59]. Depending on the structure of the phosphorus(III) derivative, the nature of the halogen X, the type and degree of substitution at the α-carbon of the carbonyl compound, and the type of function (R = H, alkyl, aryl, OR, *etc.*), one obtains one or the other, or mixtures, of two products, a phosphonate *(48)* (or a phosphonium derivative) with a new P—C bond, and the thermodynamically more stable enol ester, *(49)*, with a new P—O bond.

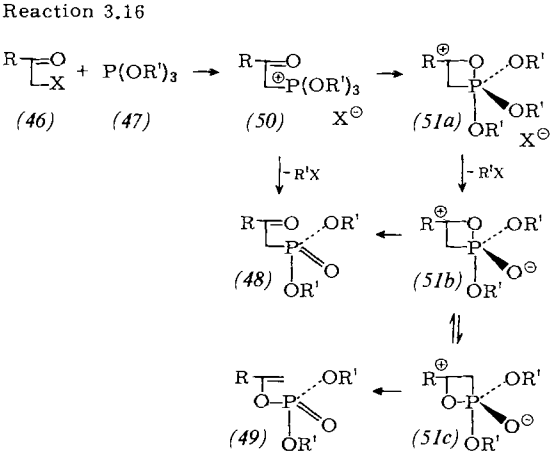
Reaction 3.15



Many mechanisms have been proposed[59] to account for various aspects of these reactions, and it has been recognized that the two reactions could proceed *via* a common intermediate or occur independently. The latter view has gained some preference over the common-intermediate hypothesis[59b].

The concepts discussed in this review lead to a further alternative for a possible solution to the problems concerning the Michaelis-Arbusov and Perkov reactions. Both reactions can result from a common phosphonium intermediate *(50)* which can either directly, or *via* *(51a)*[21b,31a,b,60] and *(51b)*, lead to the Michaelis-Arbusov product *(48)*, or through *(51c)* to the Perkov product *(49)* (see Reaction 3.16).

Reaction 3.16



The following is a statement of the Curtin-Hammett principle which may prove useful for this discussion:

In a complex kinetic system of parallel and consecutive reactions, any set of species in thermodynamic equilibrium behaves as a single kinetic entity and may be represented by any one of the species participating in the equilibrium set. This statement must be confined to systems where parallel reactions are of the same kinetic order and equilibria between participants of equilibrated species are established so rapidly relative to other participants in the kinetic system that thermodynamic equilibrium prevails at any instant of the reaction.

When the Curtin-Hammett principle applies, the ratios of the products are exclusively determined by the rate determining transition states leading to them. Such a principle is a consequence of the fact that the same type of dependence upon thermodynamic equilibrium and reaction rates exists for the free energies of the species concerned, *i.e.*, in both cases, functions of the type $\exp(-\Delta G^{\neq}/RT)$ are involved.

The dependence of the ratio of the rate of formation of the Michaelis-Arbusov product *(48)* to the Perkov product *(49)* upon the rate constants of the individual steps of Reaction 3.16 is given by Equation (3.1).

$$\frac{d[(48)]}{dt} \Big/ \frac{d[(49)]}{dt} = [k_{(50)\rightarrow(48)} \cdot k^{-1}_{(50)\rightarrow(51a)} \cdot k^{-1}_{(51c)\rightarrow(49)}] \times [-k_{(51c)\rightarrow(51b)} + k^{-1}_{(51b)\rightarrow(51c)}(k_{(51b)\rightarrow(48)} + k_{(51b)\rightarrow(51c)})(k_{(51c)\rightarrow(51b)} + k_{(51c)\rightarrow(49)})] + (k_{(51b)\rightarrow(48)} \cdot k_{(51b)\rightarrow(51c)} \cdot k^{-1}_{(51c)\rightarrow(49)}) \times (k_{(51c)\rightarrow(51b)} + k_{(51c)\rightarrow(49)})^{-1} \quad (3.1)$$

This indicates that without suitable data which permit one to cancel some of the terms in Equation (3.1), it is not possible to predict for a given α-haloketone and a set of selected reaction conditions whether the formation of *(48)* or *(49)* will prevail.

4. Mechanistic Problems Associated with the Hydrolysis of Phosphate Esters and Related Reactions

The problems associated with the hydrolysis of phosphate esters can be presented in terms of the following questions.

4.1. Are the Oxyphosphoranes Intermediates in the Hydrolyses of Phosphate Esters?

Experimental data[2, 5, 8–12, 20, 32, 61] support the assumption that oxyphosphoranes are intermediates in the hydrolysis of cyclic phosphate esters and analogous systems when the ring is five-membered. The concept of phosphorane *intermediates* in the displacement reactions of tetracoordinate phosphorus compounds originates with *McEwen et al.*[35c–g]. *Westheimer et al.*[8a] initially considered the concept of pentacoordinate *transition states* as an alternative in these reactions. Shortly thereafter, however, *Ramirez et al.*[9a, 11, 20a–d] established the former as the mechanistic interpretation for these reactions followed by a similar determination from *Westheimer et al.*[5, 8c–e, g].

The evidence for these intermediates is not as compelling in the case of phosphate esters of monofunctional aliphatic alcohols. However, the sum of all the evidence favors the general formulation of Reaction 4.1, *i.e.*, an addition-elimination mechanism where T and T′ = the tetracoordinate phosphate derivative, and N and N′ the nucleophile:

Reaction 4.1.

$$N + T \rightleftharpoons TBP \rightleftharpoons T' + N'$$

Little is known about the dynamics of this type of process; substantial differences in the relative rates of the reactions can be expected in different cases.

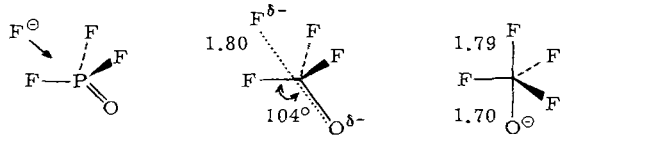
The stability of an oxyphosphorane relative to its tetracoordinate precursor or decomposition product increases with the number of P—O bonds and decreases with the accumulation of steric bulk in the immediate vicinity of the phosphorus atom. In fact, the oxyphosphoranes so far isolated contain at least two P—O bonds, and in such cases, the molecule also contains one or more four- or five-membered rings, which help reduce the local steric bulk about the phosphorus. Among acyclic oxyphosphoranes[20e–g], four or five P—O bonds are required to produce isolable but still slightly unstable oxyphosphoranes.

4.2. Is there a Well-defined and Consistent Steric Pattern for the Formation and Decomposition of the Pentacoordinate Intermediates?

All evidence points towards a mechanism in which the oxyphosphorane intermediate is formed from the tetracoordinate precursor by attack of the nucleophile at one of the tetrahedral faces, which, with regard to the skeleton of the intermediate, corresponds to an apical entry; the decomposition of the oxyphosphorane intermediate to form a tetracoordinate compound occurs *via* the departure of an apical group (see also Section 3), according to the mechanistic concept of *Ingold et al.*[35a, b] that was developed further by *McEwen et al.*[35e–g].

The postulated apical entry and departure can be supported by arguments similar to those used for the S_N2 reactions of tetrahedral carbon systems[2, 3, 4c, 5, 8, 39–44]. Moreover, this hypothesis is consistent with the observation that apical bonds in phosphorane derivatives are weaker and longer[30] than comparable equatorial bonds[33, 39, 40] having smaller force constants[31b, c].

Equatorial entry and departure has been considered as an alternative to the apical case by *Westheimer et al.*[5, 8a] and was favored by *Cram et al.*[45] for analogous processes involving sulfur compounds. An entering group approaching a molecule with a tetrahedral skeleton at one of the tetrahedral "edges" results in equatorial entry. Then, this group and two of the ligands of the tetracoordinate species become very close prior to the incoming moiety being near enough to the central atom to undergo any bonding interaction. This leads to a situation where the strong steric interactions leading to the bending motions of the two edge ligands is not compensated by a simultaneous bond formation. In the case of face attack, although the entering group now interacts with

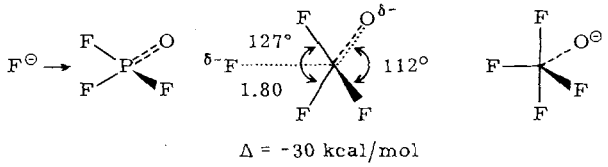


best

(2a)

(-719.4 kcal/mol)

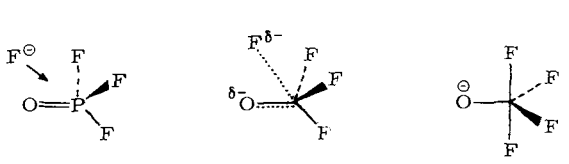
Δ = -13 kcal/mol



Δ = -30 kcal/mol

(2c)

(-689.5 kcal/mol)

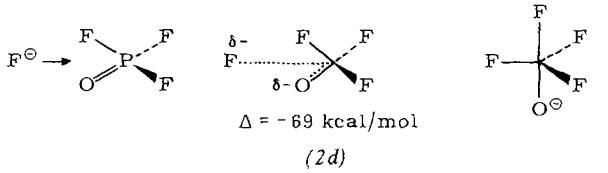


Δ = -15 kcal/mol

(2b)

(-704.5 kcal/mol)

best



Δ = -69 kcal/mol

(2d)

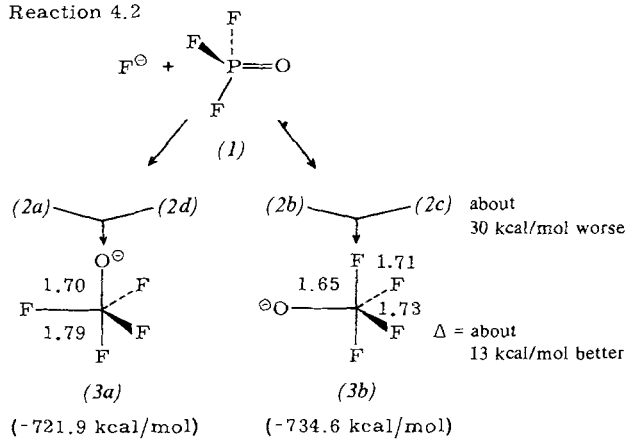
(-650.6 kcal/mol)

three ligands, this steric interaction is weaker as the route to the central atom is more open, allowing bonding to occur with less bending. This pathway, in effect, allows a more efficient rehybridization, *i. e.* less bending required, leading to more positive overlap. It would be desirable to have detailed quantitative comparisons between the apical entry-departure mechanism and its alternatives; barriers for the various types of nucleophilic attack of an $F^{\ominus}$ anion on POF_3 *(1)*, as a model system, were calculated using the CNDO/2 approximation[43b] (see also ref.[2] and literature quoted therein). Results of these calculations indicate that the barrier situations can, with some approximation, be represented by formulas *(2a–d)* shown with their binding energy in kcal/mol.

These model calculations indicate that apical attack on the FFF face *via* the barrier model situation *(2a)* is the most favorable mode of nucleophilic attack of $F^{\ominus}$ on POF_3. The latter, in comparison to attack on the OFF face [*via (2b)*] is favored by 15 kcal/mol, due in the main to increased electrostatic repulsion prior to the gain in energy upon formation of sufficient σ bond character. Equatorial attack on an FF edge *(2c)* is disfavored by 30 kcal/mol relative to apical attack *via (2a)* while FO edge attack *via (2d)* is approximately 69 kcal/mol higher in energy *vs. (2a)*.

Formation of the most stable TBP is not always favored kinetically as indicated by comparisons of *(2a)* and *(2b)* in Reaction 4.2.

Reaction 4.2



(3a)

(-721.9 kcal/mol)

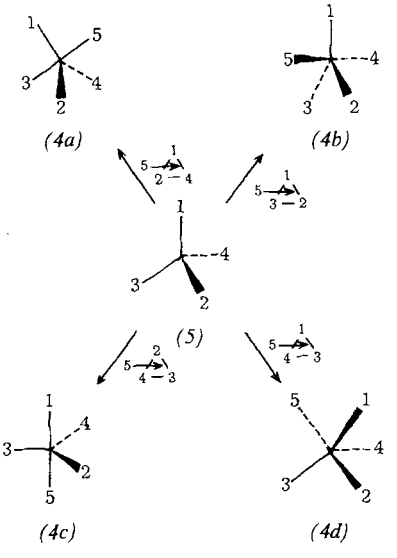
(3b)

(-734.6 kcal/mol)

By apical addition of a nucleophile, a tetracoordinate molecule *(5)* can be transformed into four different permutation isomers of a pentacoordinate intermediate, *(4a)–(4d)*.

Decomposition of a pentacoordinate molecule by the departure of an apical ligand can lead to two different

Reaction 4.3



species with a tetrahedral skeleton, which are not necessarily isomeric. In this decomposition the group with the better leaving properties departs preferentially[41–43][*].

[*] *Note added in proof:* Apical elimination and addition (re-entry of an apically eliminated ligand into one of the four "faces" of the tetracoordinate intermediate) of ligands in pentacoordinate molecules with a TBP skeleton is an irregular reorganization mechanism leading to six other (of the 20 conceivable, when all 5 ligands are different) permutation isomers. This mechanism (AEA) is resultwise equivalent to the $(TR)^2$. AEA generates the mutual interconversions of 10 each of the permutation isomers and partitions the 20 isomer set into two equivalence classes or "antipodic ensembles". For each of the species in one ensemble there exists a mirror image in the complementary emsemble. The AEA and the $(TR)^2$ are both described by the same graph consisting of two disjoint parts. These subgraphs each contain 10 points and 30 lines representing the 10 species and their 30 pairwise interactions.

4.3. Is There a Preferred Distribution of Ligands in the Oxyphosphorane Intermediate?

Quantum mechanical considerations that take into account d-orbital effects classify the ligands of a given set attached to pentacoordinate phosphorus into apicophilic and apicophobic[2]. In many cases the apicophilic ligands correspond to the most electronegative[28] ligands of the original polarity rule[39,40]. However, binding energy data (BE) of pentacoordinate phosphorus compounds calculated by the use of the CNDO/2 approximation suggest that with the aid of only one ligand property, *e.g.*, electronegativity, one can get at best a rough estimate of the relative stability of several permutation isomers[2,29]. When more than two permutation isomers are conceivable, the sequence of their relative stabilities cannot be predicted safely by the polarity rule in all cases.

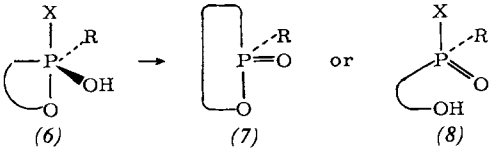
4.4. Is Apical-equatorial Placement of a Five-Membered Ring Preferred in the Pentacoordinate Intermediate of Cyclic Phosphate Hydrolysis?

Initially[8a], a pentacoordinate species with a TBP skeleton and an apico-equatorially placed five-membered ring as the activated complex was considered as one among six alternative structures for the hydrolysis of ethylene hydrogen phosphate. Reactions of the latter type were later interpreted using pentacoordinate intermediates with apico-equatorial five-membered rings as a TBP skeleton[8c], after X-ray crystallographic studies of cyclic oxyphosphorane derivatives with five-membered rings had shown that the rings are attached apically-equatorially to the TBP molecular skeleton[32]. The same is found for cyclic oxyphosphoranes with four-membered rings[31b]. A four-membered ring with a 90° TBP apical-equatorial angle is definitely less strained than that with a deformed 120° TBP diequatorial angle[2,29]. Similar arguments apply to the five-membered ring situation, as can be shown by calculations on suitable model compounds[2,29]. The total strain appears as the sum of the contributions of the deformations of all members of the ring, and includes also the conformational contributions[62]. These considerations suggest that six-membered rings should preferentially be placed diequatorially on the TBP skeleton. However, a thorough experimental and theoretical study of six-membered cyclic oxyphosphoranes is required to determine the generality of this conclusion.

4.5. Are Rings Preferentially Preserved or Opened Upon Decomposition of Cyclic Oxyphosphoranes?

There is no general answer to this question. The fate of the ring is closely dependent upon the chemical constitution of the oxyphosphorane derivative and upon the specific reaction conditions whose influence varies from case to case[*]. Much experimental evidence exists concerning the acid and base catalyzed hydrolyses of cyclic phosphate and phosphonate esters in aqueous media, and they have been extensively discussed[5,6,8,10,12]. However, this effort has not yielded a consistent and general picture of the fate of the ring in these compounds. Valuable information can be obtained from studies on the hydrolyses of cyclic phosphate esters[9a,61c,d,h], and of isolable cyclic oxyphosphoranes[9,20a,b,d,61a–d,f] with limited amounts of water in aprotic solvents; cf. Sections 6 and 7. The transformations of the five-membered cyclic oxyphosphoranes into the tetracoordinate phosphate under these conditions generally proceed with preservation of the ring[9,20a,d,61a–d,f]; cf. *(6)*→*(7)* in Reaction 4.4. Sometimes this tendency for the preservation of five-membered rings during the decrease in coordination number is obscured by rapid secondary reactions among the products that result from the primary reaction stage, *i.e.*, the initially formed cyclic phosphate ester is subsequently transformed into an acyclic phosphate *(8)*.

Reaction 4.4



4.6. What Happens to the Phosphoryl Oxygen (P=O) when the Tetracoordinate Phosphate is Transformed into an Oxyphosphorane Intermediate?

The phosphoryl oxygen of the phosphate can be transformed into an apical or an equatorial ligand of the corresponding oxyphosphorane derivative. Depending on the protonation or lack of it during the addition step, this transformation can result in a hydroxyl group or in an anionic oxygen ligand.

The calculated BE data of the mono- and dianions of various suitable polyhydroxy phosphorane models[2,29] demonstrate clearly that the $O^{\ominus}$ ligands have a pronounced tendency to occupy equatorial positions, as had been already assumed[12] from an application of the polarity rule (see Section 4.3). The equatorial hydroxyl groups of polyhydroxy phosphoranes are, by many orders of magnitude, more acidic than the corresponding apical hydroxyl groups. Hence, one should expect that oxyphosphorane derivatives arise from tetracoordinate phosphates *via* two different mechanisms.

Mechanism 4.6.1.

If sufficient protons are available in the reaction medium, and if the molecule is free from any constraint that requires the apical placement of a particular ligand[63], then the

[*] *Note added in proof:* In general, it seems that the collapse of an oxyphosphorane with the loss of *methanol* and the retention of the ring is favored over the collapse with ring opening (see Section 6). The apparent exception to this rule encountered in the hydrolysis of dimethyl acetoin phosphate (Section 5.2) may be due to the rather special nature of the corresponding oxyphosphorane intermediate; in this intermediate one of the ring carbons is a hemiacetal analog and the initial collapse of the oxyphosphorane probably involves C—O bond rupture and not the P—O rupture. The dimethyl acetoin phosphate case does not represent, strictly, a comparison of the tendency of the ring to be retained or opened in the collapse of an oxyphosphorane by departure of an oxygen ligand from TBP phosphorus. When the collapse of an oxyphosphorane involves the loss of *water* and the retention of the ring, that pathway seems to be slightly disfavored over the pathway for ring opening (see Section 5.3). These situations are further discussed in the appropriate Sections.

phosphoryl oxygen of the phosphate will appear as an apical OH in the TBP because in this process all participating components of the incipient oxyphosphorane are collinear (*i.e.*, the incoming nucleophile, as well as the P and the phosphoryl O). A hydroxyl group is also more apicophilic than an alkoxyl group.

Mechanism 4.6.2.

If there is insufficient proton supply, or if some overriding constraint in the molecule (*e.g.*, the presence of a five-membered ring) forces one of the ligands to be apical, then one should expect that the phosphoryl oxygen will appear as an $O^{\ominus}$ ligand in an equatorial position of the TBP skeleton.

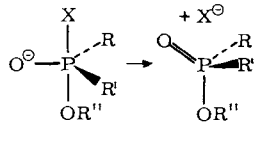
4.7. Which Conditions Promote the Formation of a Tetracoordinate Phosphorus Compound from a Pentacoordinate Oxyphosphorane Derivative?

Any set of conditions which allows the departure of an apical ligand from the TBP phosphorane *without charge separation* should facilitate the decomposition of the phosphorane. This condition can be met both in solvents that are capable of supporting a charge on a molecule, and in those that are incapable of supporting a charge on a molecule.

4.7.1. The usual media that can support a charge on a molecule are protic solvents of variable polarity, such as water and alcohols. In protic solvents one can conceive three extreme situations.

1. When there is proton deficiency, as in Reaction 4.5, the negative charge on the equatorial $O^{\ominus}$ ligand of the TBP is transferred to the departing apical ligand X, *(9)*→*(10)*.

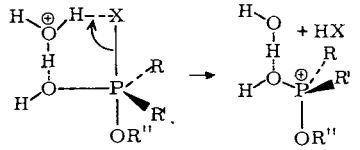
Reaction 4. 5



(9) *(10)*

2. When protons are readily available, as in Reaction 4.6, a proton from the solvent-oxonium is transferred to the decomposing oxyphosphorane, *i.e.*, the positive charge is transferred from oxygen to phosphorus, *(11)*→*(12)*.

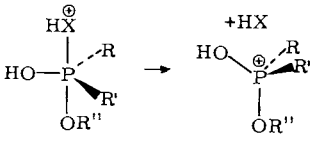
Reaction 4. 6



(11) *(12)*

3. When there is proton abundance, and when the nature of the ligand X in the phosphorane favors its protonation, one obtains the case shown in Reaction 4.7. Now the positive charge is transferred from the ligand X to phosphorus, *(13)*→*(14)*.

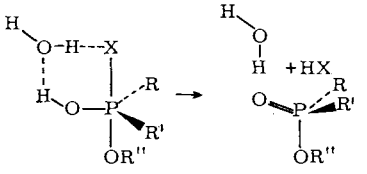
Reaction 4. 7



(13) *(14)*

4.7.2. The media that cannot support a charge on a molecule are to be found among aprotic solvents of relatively low polarity. In this situation small amounts of water may yield hydrogen bonded adducts of the oxyphosphorane involving one or more water molecules, *e.g.*, *(15)* of Reaction 4.8. Proton transfers which avoid charge separation may still occur within these adducts, *(15)*→*(16)*.

Reaction 4. 8



(15) *(16)*

In Reactions 4.5–4.8 the phosphoryl oxygen of the product originates from equatorial $O^{\ominus}$ or HO groups. In the cases of Reactions 4.6–4.8 the original hydroxyl group could have been apical in the TBP phosphorane as well.

4.8. Do the Oxyphosphorane Intermediates Undergo Permutational Isomerizations; and, if so, by what Mechanism?

To apply the principles set forth in Sections 4.1 through 4.8 one must introduce the further concept of permutational isomerization of the TBP phosphorane intermediate. It is mandatory to distinguish between *regular* and *irregular permutation isomerizations*[2,29]. Regular processes occur without bond making and breaking, with preservation of all the proximity relationships defined by the bond system and maintenance of coordination number. Regular processes are possible only in flexible molecular skeletons. Regular reorganization processes of molecules with monocentric skeletons, such as the pentacoordinate phosphoranes, correspond in principle to the conformational interconversions of molecules with polycentric skeletons, *e.g.*, the ethane derivatives; the differences are due to different types of skeletal flexibility[2,29].

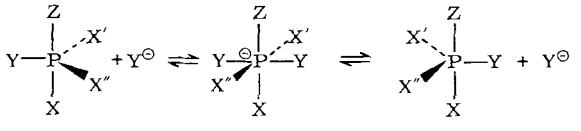
Irregular reorganization processes, in contrast to the regular ones, proceed with opening and closing of covalent bonds *via* intermediates which differ from the initial and final compounds in their coordination numbers[21,23–27,29a]. The regular permutational isomerization of stable phosphoranes and of postulated phosphorane intermediates have been the subject of recent intensive studies and discussion[2,3,5,26,27,29–31,38,45,64–68]. Of all the conceivable mechanistic alternatives which are given by the subclasses of S_5[2,29] only two can be accepted as providing reasonable pathways for the regular reorganization processes of pentacoordinate molecules with a TBP skeleton, namely *Berry pseudorotation*[38] (BPR)

and the *simple and multiple turnstile rotations*[2, 29] (TR). In some cases, the TR mechanism provides the only interpretation of the experimental data[2, 29]. Cyclic phosphorane derivatives where the phosphorus is a part of a four- or five-membered ring (except spiro compounds) undergo only such *TR processes in which the ring participates as the pair.*

The irregular rearrangement processes of phosphorane derivatives occur *via* tetracoordinate or hexacoordinate species. When rearrangement processes of phosphorane derivatives are open to investigation by NMR, it is possible, in favorable cases, to discriminate experimentally between regular and irregular processes. If, for example, there is a spin-spin interaction between a ligand and the phosphorus central atom, then this coupling is not destroyed by regular processes, but disappears during irregular processes, unless these are intramolecular and proceed extremely rapidly.

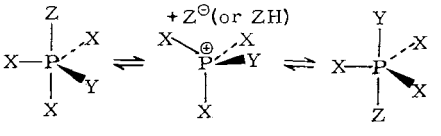
Possible irregular permutation isomerizations of oxyphosphorane intermediates in the hydrolyses of phosphate esters and related reactions should not be overlooked. There are many experimental observations that can be interpreted solely on the basis of irregular isomerizations of the intermediates (see Section 2.2). Base catalysis favors irregular processes proceeding *via* higher coordination intermediates (*e.g.*, see Reaction 4.9). Thermal or acid catalyzed reactions are more likely to involve irregular processes *via* intermediates that are lower in coordination number (Reaction 4.10).

Reaction 4.9



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

Reaction 4.10



(19) *(20)* *(21)*

It seems quite likely that under certain conditions in the hydrolyses of phosphate esters, oxyphosphorane intermediates are capable of adding hydroxide ions to form hexacoordinate intermediates (or transition states). If hexacoordinate species are indeed involved (cf. Section 2), the *Selection Rules*[5, 8c, d] postulated for the hydrolyses of cyclic phosphates lose their basis. The kinetic analysis of the hydrolysis of phosphate esters to be presented in Section 5 shows the added complexity that is introduced by the involvement of hexacoordinate species in these reactions. Even neglecting those species, the kinetic systems are quite complex, and it will be shown that kinetic observations *per se* are insufficient to justify the proposed Selection Rules[5, 8c, d] and to resolve the troublesome questions raised by the previous use of the Principle of Microscopic Reversibility[3, 5]. However, it should be emphasized that some elements of the Selection Rules, notably apical entrydeparture and ligand polarity, are quite valid and have been incorporated into the concept developed in this Review.

4.9. What is the Effect of Metal Ions on the Behavior of Tetra- and Pentacoordinate Phosphoric Acid Derivatives?

Biochemically important derivatives of phosphoric acid exist, under physiological conditions, largely as anions. These anions have little tendency to react with nucleophiles, in part due to decreased electrophilicity, in part due to the fact that in polyphosphates the leaving group porperties of the phosphate moiety are substantially decreased by the negative charge *vs.* the undissociated compounds. It is widely accepted that metal ions, such as Mg^{2+}, affect the reactivity of these phosphoric acid derivatives by neutralizing negative charges thus improving their tendency to react with nucleophiles[7, 29d, 69, 70]. Indeed, it has been suggested[7d, h] that the chief function of magnesium ion in promoting the reactions of polyphosphates is its ability to "neutralize" the negative charges of the polyphosphate. This concept, however, is not always sufficient for the interpretation of the observations; for example, Ca^{2+} and Mg^{2+} do not cause a significant rate increase in the hydrolysis of ATP[71] at pH 8.5 to 8.8.

The order of stability of the 1:1 complexes of metal ions and phosphate ligands[72] like AMP, ADP, ATP is: $Ba^{2+} \approx Sr^{2+} \approx Ca^{2+} \approx Mg^{2+} < Mn^{2+} \approx Fe^{2+} \approx Co^{2+} \approx Ni^{2+} \approx Cu^{2+} \approx Zn^{2+}$. This order is independent of the nature of the phosphate[72], as shown by the comparable stability of complexes of HPO_4^{2-} and $HP_3O_{10}^{4-}$. The nucleoside moiety in nucleotides seems to have little effect on the stability of the complexes with metal ions[72]. The oxygen-containing donor-ligands, unlike the nitrogen and sulfur analogs, do not effectively discriminate among the various metal ions, as far as complex stability is concerned[72].

For the discussion of the possible role of metal ions in phosphate and pyrophosphate chemistry, one must take into account the formation of oxyphosphorane intermediates and the effect of the polarity of the reaction medium on the interaction of metal ions with tetracoordinate and pentacoordinate phosphorus derivatives. For example, it is conceivable that the coordination of a metal cation with the anions of oxyphosphoranes, under certain conditions, could affect the relative stabilities of the various permutational isomers of the latter and their interconversion barriers.

These effects will be discussed in a subsequent review dealing with the behavior of AMP, ADP, and ATP, and related systems.

4.10. Summary of Rules

The interpretation of the available data on the hydrolysis of phosphate esters and related compounds is achieved by the consistent application of the eight postulates discussed in this Section. The interpretation of the data on reduction

of phosphane oxides and on displacement reactions of phosphonium compounds involves the same postulates, with minor variations, which depend on the circumstance that several of the ligands are carbon atoms rather than oxygen atoms. This affects primarily the relative stability of the phosphorane intermediates, the placement of ligands in the TBP, the ability of ligands to act as leaving groups, and the barriers for the permutational isomerizations of the TBP molecules; for future reference, the eight rules that evolve from the present analysis can be summarized as follows:

1. Intermediacy of oxyphosphoranes.

2. Apical entry-departure rule.

3. The polarity rule modified by taking into account d-orbital effects and ligand-ligand interactions.

4. Exclusive apical-equatorial placement of five-membered and four-membered rings in oxyphosphoranes, in contrast to the preferred diequatorial placement of six-membered rings.

5. Preferential retention of rings in decompositions of cyclic oxyphosphoranes.

6. Equatorial placement of anionic oxo ligands, apical or equatorial placement of hydroxyl groups, in oxyphosphoranes.

7. Avoidance of charge-separation in decomposition of oxyphosphoranes.

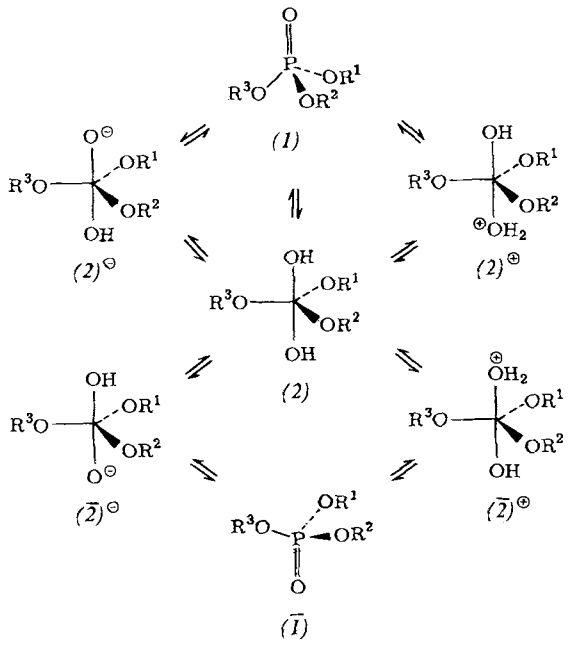
8. Permutational isomerization of oxyphosphorane by regular and irregular processes. Regular permutational isomerizations may occur by the TR or BPR mechanism for open chain systems; however, these processes must (with the exception of spiro compounds) go *via* TR for cyclic systems. We observe exclusive involvement of the four- and five-membered rings as the pair and normally the six-membered ring as the trio in the pair-trio combination of the TR-mechanism in oxyphosphoranes. Irregular permutational isomerizations occur *via* intermediates (or transition states) with coordination number six (base-catalyzed), and *via* intermediates with coordination number four (thermal or acid-catalyzed).

5. Kinetic Data in Mechanistic Studies of Hydrolyses of Phosphate Esters

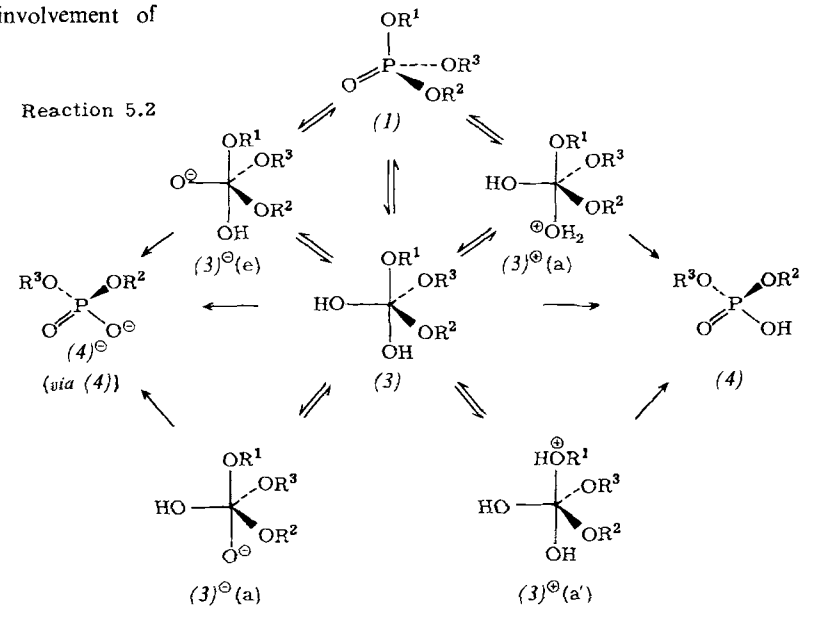
5.1. General Considerations. Hydrolyses of Trimethyl Phosphate and Ethylene Methyl Phosphate

The statements set forth in Section 4 lead to the general formulation of the hydrolyses of phosphate esters shown in Reactions 5.1 through 5.5.

Reaction 5.1

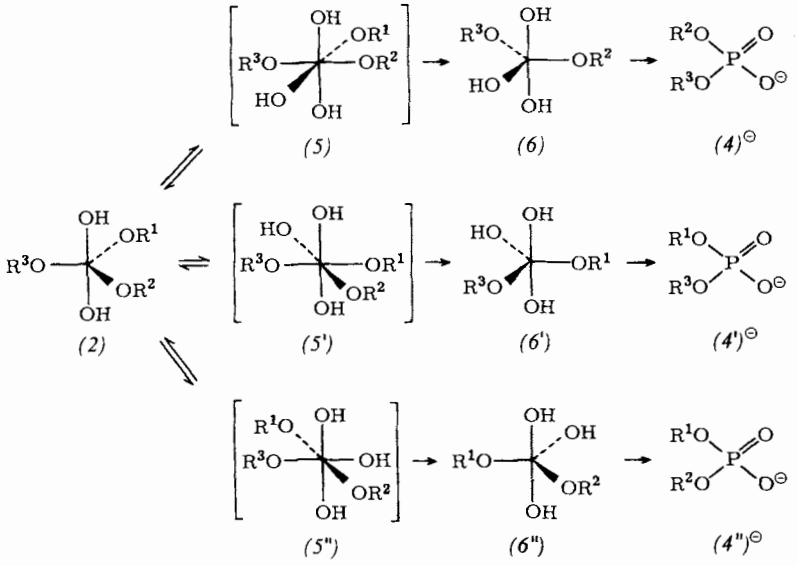


Reaction 5.2



In these reactions, hydroxide ions or water are introduced at the skeletal tetrahedral face opposite either the phosphoryl oxygen (Reaction 5.1), or protonated phosphoryl oxygen, or one of the alkoxide groups (Reaction 5.2) of the ester. The key oxyphosphoranes are *(2)* (Reaction 5.1) and *(3)* (Reaction 5.2), with two hydroxyl ligands apical, or one apical and one equatorial, respectively. Reaction

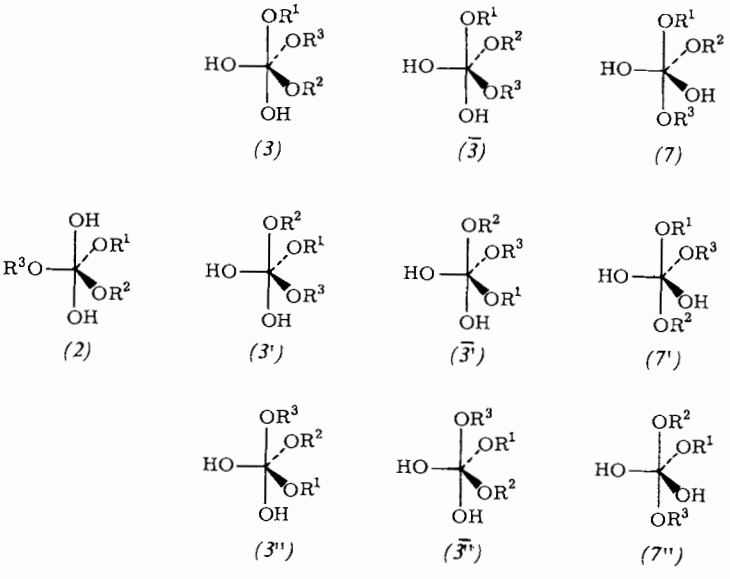
Reaction 5.3



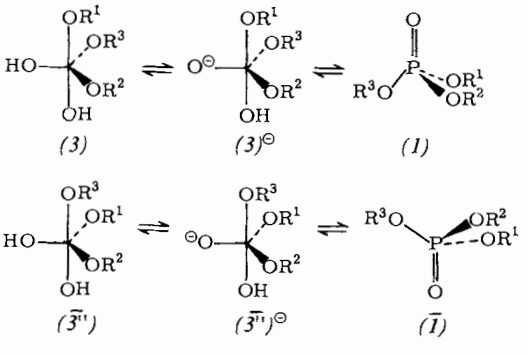
5.1 is an oxygen-exchange *(1)* → *(Ī)*, and Reaction 5.2 is a hydrolysis, *(1)* → *(4)*, $(4)^{\ominus}$. The alkaline oxygen exchange is disfavored because it requires the placement of $O^{\ominus}$ in an apical position, *(1)* → $(2)^{\ominus}$, in violation of the modified polarity rule. The ionization step, *(3)* → $(3)^{\ominus}$ (a) in Reaction 5.2 is disfavored for the same reason.

If octahedral transition states with hexacoordinate phosphorus are also involved under certain conditions, with collinear (opposed) entering and departing groups, the formation of hydrolysis products, $(4)^{\ominus}$, $(4')^{\ominus}$, $(4'')^{\ominus}$, *via* the TBP *(2)* must also include the pathways shown in Reaction 5.3. If species with hexacoordinate phosphorus are intermediates, and undergo reorganizations of their own, and/or are capable of losing either one of the various ligands to return to a TBP phosphorane, then additional steps must be included, *e.g.*, *(5')* → *(6')* → $(4')^{\ominus}$.

Reaction 5.4



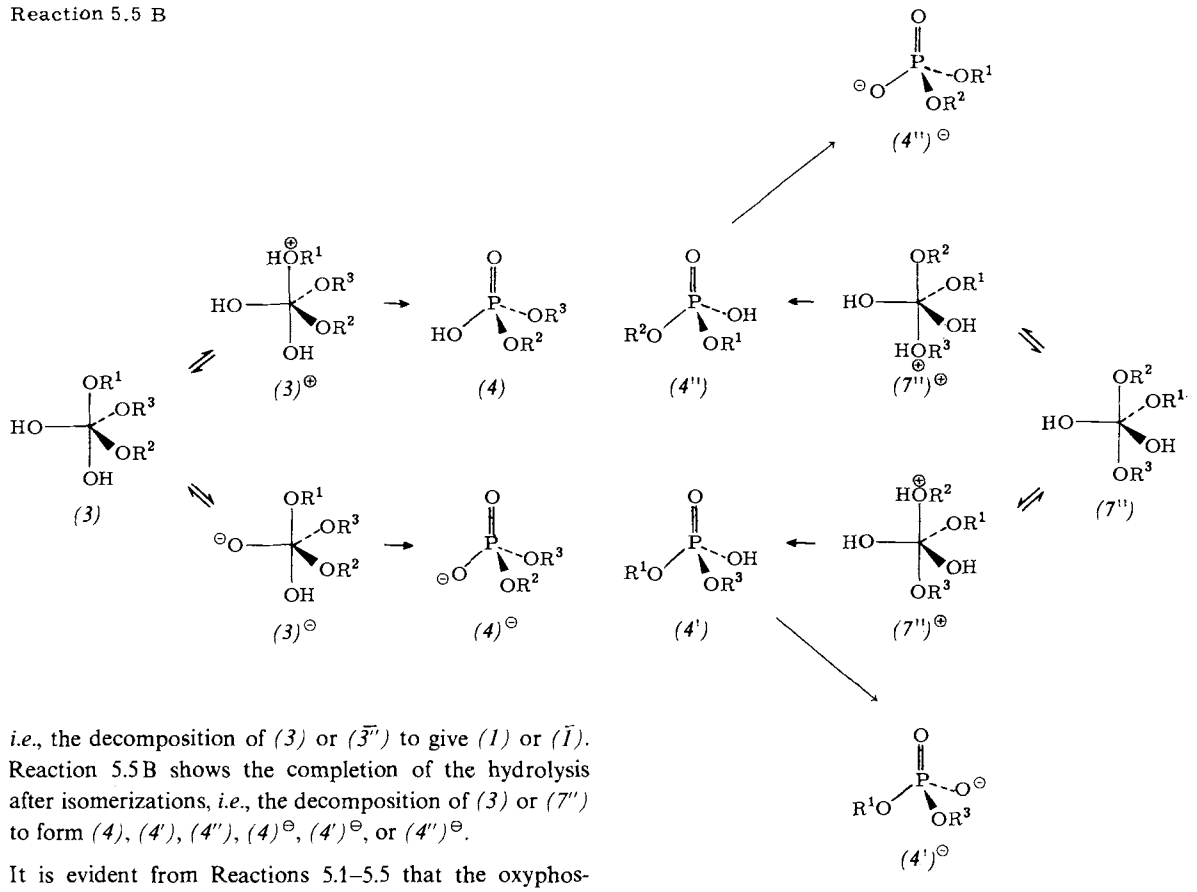
Reaction 5.5A



Reaction 5.4 represents the set of permutational isomers of the neutral TBP phosphoranes that originate from *(1)* and water. The interconversion of these isomers can occur by the simple and multiple TR processes and, if rings are absent from the TBP, also by the BPR process[2,29].

Reaction 5.5A is the completion of the oxygen-exchange after the permutational isomerizations (cf. Reaction 5.4),

Reaction 5.5 B

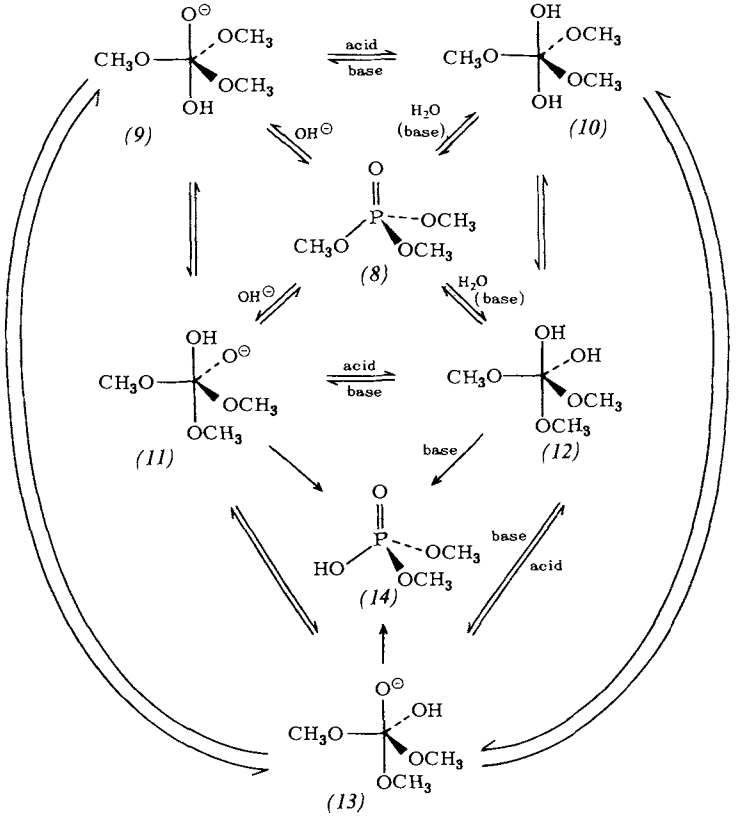


i.e., the decomposition of *(3)* or *(3‴)* to give *(1)* or *(1̄)*. Reaction 5.5B shows the completion of the hydrolysis after isomerizations, *i.e.*, the decomposition of *(3)* or *(7″)* to form *(4)*, *(4′)*, *(4″)*, $(4)^{\ominus}$, $(4')^{\ominus}$, or $(4'')^{\ominus}$.

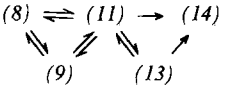
It is evident from Reactions 5.1–5.5 that the oxyphosphorane-intermediate hypothesis gives rise to a rather complex kinetic system of consecutive and parallel reactions in the hydrolyses of phosphate esters. A comparison of observed reaction rates cannot lead to valid mechanistic conclusions, unless there is reasonable assurance that, in a set of consecutive reactions, one known step is much slower than all others and hence is rate determining, and in a given set of competing parallel reactions, one of the competing sequences of reactions is much faster than all the others and hence the latter can be neglected. Without such assurances even the observed rate of such seemingly simple processes as the hydrolysis of trimethyl phosphate in weakly alkaline solution must be treated as a fairly complex function of 27 different rate processes (see Reaction 5.6A). In very strongly alkaline solution, where hexacoordinate transition states or intermediates should also be considered (cf. Reaction 5.3), the situation is even more complicated.

As a consequence of this complexity, it seems advisable to reexamine the far-reaching conclusions that have been drawn previously on the basis of comparison of the rates of hydrolysis of these compounds[5,8], in order to determine which are valid and which need modification.

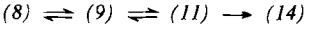
Reaction 5.6A



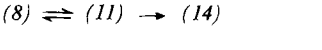
Reaction 5.6B



Reaction 5.6C



Reaction 5.6D



Consider the *alkaline hydrolysis* of trimethyl phosphate *(8)→(14)* in the light of the premises set forth in Section 4. In this case, Reaction 5.6A is simplified to Reaction 5.6B with 10 rate constants, since the reactions with H_2O and the protonations are neglected *vs.* the reactions with $HO^{\ominus}$

The application of the Bodenstein theorem to Reaction 5.6B:

$$\frac{d[(9)]}{dt} = \frac{d[(11)]}{dt} = \frac{d[(13)]}{dt} = 0 \qquad (5.6a)$$

results in Equation (5.6b), which is still of some complexity.

$$\begin{aligned}\frac{d[(14)]}{dt} = [(8)][OH^{\ominus}]\cdot k_{hydrol,obs.} = [(8)][OH^{\ominus}][&k_{(11)\to(14)} \\ &+k_{(13)\to(14)}\cdot k_{(11)\to(13)}(k_{(13)\to(11)}+k_{(13)\to(14)})^{-1}] \\ &\times k_{(8)\to(11)}k_{(9)\to(11)}(k_{(9)\to(8)}+k_{(9)\to(11)})^{-1}[(k_{(11)\to(8)} \\ &+k_{(11)\to(9)}+k_{(11)\to(13)}+k_{(11)\to(14)}) \\ &-k_{(11)\to(13)}k_{(13)\to(11)}(k_{(13)\to(11)}+k_{(13)\to(14)})^{-1} \\ &-k_{(11)\to(9)}k_{(9)\to(11)}(k_{(9)\to(8)}+k_{(9)\to(11)})^{-1}]^{-1}\end{aligned} \qquad (5.6b)$$

Further simplifications can be achieved by neglecting one of the unfavorable TBP with an apical oxygen anion, namely *(13)*. One can now consider two alternate additional simplifications. The first is the exclusive direct formation of the other unfavorable TBP *(9)* with an apical oxide anion, followed by a permutational isomerization and decomposition to dimethyl phosphate *(14)*, as shown in Reaction 5.6C. The isomerization *(9)⇄(11)* must involve two simple TR or BPR or one $(TR)^2$, *e.g.*, with OH and OCH_3 as the pair[2,46]. The kinetic consequences would be given by Equation (5.6c):

$$\begin{aligned}k_{hydrol,obs.} = &k_{(11)\to(14)}\cdot k_{(8)\to(9)}\cdot k_{(9)\to(11)} \\ &\times[(k_{(11)\to(9)}+k_{(11)\to(14)})(k_{(9)\to(8)}+k_{(9)\to(11)}) \\ &-k_{(9)\to(11)}\cdot k_{(11)\to(9)}]^{-1}\end{aligned} \qquad (5.6c)$$

which reduces to Equation (5.6c') if *(9)⇄(11)* is rate determining:

$$k_{hydrol,obs.} = k_{(8)\to(9)}\cdot k_{(9)\to(11)}\cdot k^{-1}_{(9)\to(8)} \qquad (5.6c')$$

The second and more logical approximation is to assume an exclusive direct formation of the most stable TBP *(11)* with an equatorial oxide anion, followed by direct decomposition to dimethyl phosphate *(14)* without any intervening permutational isomerization (cf. Reaction 5.6D). The kinetic consequences are those in Equation (5.6d):

$$k_{hydrol,obs.} = k_{(11)\to(14)}\cdot k_{(8)\to(11)}\cdot(k_{(11)\to(8)}+k_{(11)\to(14)})^{-1} \qquad (5.6d)$$

If further $k_{(11)\to(14)} \gg k_{(11)\to(8)}$, one obtains Equation (5.6d'):

$$k_{hydrol,obs.} = k_{(8)\to(11)} \qquad (5.6d')$$

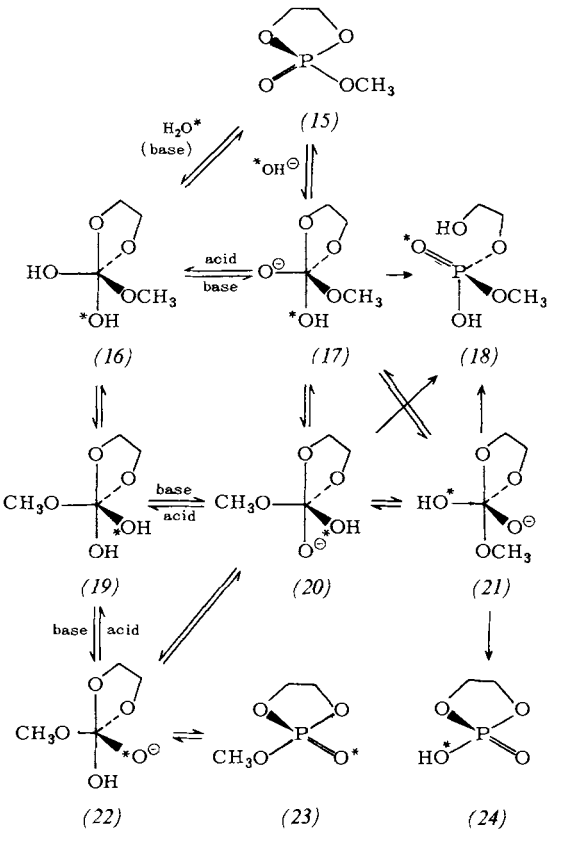
If, however, $k_{(11)\to(8)} \gg k_{(11)\to(14)}$, the result is Equation (5.6d''):

$$k_{hydrol,obs.} = k_{(11)\to(14)}\cdot k_{(8)\to(11)}\cdot k^{-1}_{(11)\to(8)} \qquad (5.6d'')$$

Evidently, even under the extreme simplifications contained in Reaction 5.6D, the $k_{hydrol,obs.}$ in the alkaline hydrolysis of trimethyl phosphate provides straightforward information only if the partition of the TBP phosphorane *(11)* between product and reactant strongly favors the product as shown in Equation (5.6d').

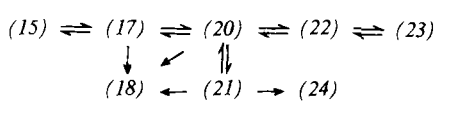
Consider now the much studied[5,8b,e] hydrolysis of methyl ethylene phosphate in *weakly alkaline solution*. Without simplifications the picture of Reaction 5.7A is kinetically quite complex.

Reaction 5.7A

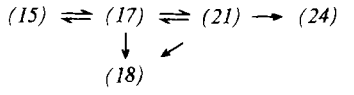


If one neglects the reaction of H_2O and the proton transfers, the picture is simplified to that of Reaction 5.7B.

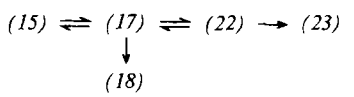
Reaction 5.7B



Reaction 5.7C



Reaction 5.7D



The kinetic expressions that give the rate of hydrolysis with ring opening, *(15)→(18)*, and with ring retention (exocyclic hydrolysis), *(15)→(24)*, and the rate of ex-

change of the phosphoryl oxygen with the solvent, *(15)→(23)*, are shown in Equations (5.7a), (5.7b), and (5.7c), respectively. These are still complex expressions as can be seen by developing the term P as shown in Equation (5.7d). No quantitative understanding of the factors that determine the rates of these hydrolyses, and the ratio of the rates of the three processes of interest, *i.e.*, the formation of *(18)*, *(24)*, and *(23)*, can be gained in this manner, *i.e.*, from $k_{(18)\,\mathrm{obs.}}$, $k_{(24)\,\mathrm{obs.}}$, $k_{(23)\,\mathrm{obs.}}$, even after the simplifications that led to Reaction 5.7 B.

$$\frac{d[(18)]}{dt} = [(15)][OH^{\ominus}]\cdot P^{-1}\cdot k_{(17)\to(18)}(P\cdot k_{(15)\to(17)}+k_{(20)\to(17)}) \times(k_{(17)\to(15)}+k_{(17)\to(18)}+k_{(17)\to(20)})^{-1} + k_{(20)\to(18)}+k_{(20)\to(21)}\cdot k_{(21)\to(18)} \times(k_{(22)\to(20)}+k_{(22)\to(23)})^{-1} \quad (5.7a)$$

$$\frac{d[(23)]}{dt} = [(15)][OH^{\ominus}]\cdot P^{-1}\cdot k_{(22)\to(23)}\cdot k_{(20)\to(22)} \times(k_{(22)\to(20)}-k_{(22)\to(23)})^{-1} \quad (5.7b)$$

$$\frac{d[(24)]}{dt} = [(15)][OH^{\ominus}]\cdot P^{-1}\cdot k_{(21)\to(24)}\cdot k_{(20)\to(21)} \times(k_{(21)\to(18)}+k_{(21)\to(20)}+k_{(21)\to(24)})^{-1} \quad (5.7c)$$

with

$$P = k_{(15)\to(17)}^{-1}\cdot k_{(17)\to(20)}^{-1}[(k_{(17)\to(15)}+k_{(17)\to(18)} + k_{(17)\to(20)})\{(k_{(20)\to(17)}+k_{(20)\to(18)}+k_{(20)\to(21)}+k_{(20)\to(22)}) - k_{(20)\to(21)}\cdot k_{(21)\to(20)}(k_{(21)\to(18)}+k_{(21)\to(20)}+k_{(21)\to(24)})^{-1} - k_{(20)\to(22)}\cdot k_{(22)\to(20)}(k_{(22)\to(20)}-k_{(22)\to(23)})^{-1}\} - k_{(17)\to(20)}\cdot k_{(20)\to(17)}] \quad (5.7d)$$

To treat this system further, one must resort to additional simplifications, for example, those which lead to the picture of Reaction 5.7C (see above). Now, one neglects the oxygen exchange *(15)→(23)*, and assumes that ring opening, *(15)⇄(17)→(18)*, occurs exclusively by the most direct pathway without permutational isomerization. Exocyclic hydrolysis, *(15)⇄(17)⇄(21)→(24)*, is assumed to occur exclusively after one reasonable permutational isomerization that preserves the equatorial placement of the oxide anion. The kinetic expressions that result from Reaction 5.7C are shown in Equations (5.7e)–(5.7g).

$$\frac{d[(18)]}{dt} = [OH^{\ominus}][(15)]R^{-1}[k_{(21)\to(18)}+(k_{(21)\to(17)}+k_{(21)\to(18)} + k_{(21)\to(24)})\cdot k_{(17)\to(21)}^{-1}\cdot k_{(17)\to(18)}] = [OH^{\ominus}][(15)]k_{\mathrm{obs.}(18)} \quad (5.7e)$$

$$\frac{d[(24)]}{dt} = [OH^{\ominus}][(15)]k_{(21)\to(24)}\cdot R^{-1} = [OH^{\ominus}][(15)]k_{\mathrm{obs.}(24)} \quad (5.7f)$$

with

$$R = k_{(15)\to(17)}^{-1}[(k_{(17)\to(15)}+k_{(17)\to(18)}+k_{(17)\to(21)})(k_{(21)\to(17)} + k_{(21)\to(18)}+k_{(21)\to(24)})k_{(17)\to(24)}^{-1}-k_{(21)\to(17)}] \quad (5.7g)$$

The ratio of the rates of ring-opening *(15)→(18)* to ring-retention *(15)→(24)* is given by Equation (5.7h)

$$k_{\mathrm{obs.}(18)}/k_{\mathrm{obs.}(24)} = [k_{(17)\to(21)}\cdot k_{(21)\to(18)} + (k_{(21)\to(17)}+k_{(21)\to(18)}+k_{(21)\to(24)}) \times k_{(17)\to(18)}](k_{(17)\to(21)}\cdot k_{(21)\to(24)})^{-1} \quad (5.7h)$$

All that can be concluded from the experimental observation that $k_{\mathrm{obs.}(18)} \gg k_{\mathrm{obs.}(24)}$ is that either $k_{(17)\to(18)} \ll k_{(17)\to(21)}$, or that $k_{(21)\to(18)} \gg (k_{(21)\to(17)}+k_{(21)\to(24)})$ where $k_{(17)\to(18)} \approx k_{(17)\to(21)}$.

Detailed knowledge concerning the complete dynamics for a system of consecutive and parallel reactions would allow one to predict the kinetic behavior of the system. Conversely, it is possible to derive detailed conclusions from observed rates of complex systems only in some exceptional cases. From this it follows that the mere comparison of observed reaction rates does not provide valuable information.

The fact that *(15)→(23)* is slow relative to *(15)→(18)* + *(24)* could, for example, be interpreted by a simplification that produces the picture of Reaction 5.7D (see above). In this interpretation, one imagines a simultaneous proton transfer and permutational isomerization, *(17)→(22)*, which results in the kinetic expressions of Equations (5.7i)–(5.7k).

$$k_{\mathrm{obs.}(18)} = S^{-1}\cdot k_{(17)\to(18)}\cdot k_{(15)\to(17)} \quad (5.7i)$$

$$k_{\mathrm{obs.}(23)} = k_{(22)\to(23)}\cdot k_{(15)\to(17)}\cdot k_{(17)\to(22)} \times S^{-1}(k_{(22)\to(17)}+k_{(22)\to(23)})^{-1} \quad (5.7j)$$

with

$$S = k_{(17)\to(15)}+k_{(17)\to(18)}+k_{(17)\to(22)}-k_{(22)\to(17)}\cdot k_{(17)\to(22)} \times(k_{(22)\to(17)}+k_{(22)\to(23)})^{-1} \quad (5.7k)$$

The ratio of the rates of hydrolysis with ring opening, *(15)→(18)*, and of oxygen-exchange, *(15)→(23)*, would be given by Equation (5.7l):

$$k_{\mathrm{obs.}(18)}/k_{\mathrm{obs.}(23)} = k_{(17)\to(18)}\cdot k_{(22)\to(23)}^{-1}\cdot k_{(17)\to(22)}^{-1} \times(k_{(22)\to(17)}+k_{(22)\to(23)}) \quad (5.7l)$$

Since it is experimentally observed that $k_{\mathrm{obs.}(18)} \gg k_{\mathrm{obs.}(23)}$, one may conclude that either $k_{(17)\to(18)} \gg k_{(17)\to(22)}$ where $k_{(22)\to(17)} \ll k_{(22)\to(23)}$, or that $k_{(17)\to(18)} \gg k_{(22)\to(23)}$ where $k_{(22)\to(23)} \ll k_{(22)\to(17)}$ and $k_{(17)\to(22)} \approx k_{(22)\to(17)}$.

This analysis shows that a mechanistic interpretation of the hydrolyses of trimethyl phosphate (Reaction 5.6) and methyl ethylene phosphate (Reaction 5.7) from the available experimental kinetic data must be based on a series of simplifications and approximations which have not been subject to test. It is even more difficult to derive sound mechanistic conclusions from a comparison of the rate data for the two reactions; *i.e.*, to *interpret the differences in the reaction rates for Reaction 5.6 and Reaction 5.7*. Let us assume that the behavior of the acyclic phosphate is well described by the approximations that give Reaction 5.6C from Reaction 5.6A, and that of the cyclic phosphate by the approximations that give Reaction 5.7C from Reaction 5.7A. In the cyclic case, ring opening is faster than ring retention, *i.e.*, $k_{\mathrm{obs.}(18)} \gg k_{\mathrm{obs.}(24)}$ and Equation (5.7f) is neglected *vs.* Equation (5.7e). The pertinent equation for the acyclic case is Equation (5.6c'), since the isomerization *(9)⇄(11)* is assumed to be rate determining in Reaction 5.6C. One could attribute the observed faster

hydrolysis with ring-opening *(15)→(18)* relative to the hydrolysis of trimethyl phosphate *(8)→(14)*, $k_{obs.(18)} \gg k_{obs.(14)}$, to the operation of one, two, or all three of the following factors:

1. The TBP intermediate is formed much faster in the cyclic than in the acyclic case; *i.e.*, $k_{(15)\rightarrow(17)} \gg k_{(8)\rightarrow(9)}$.

2. The decomposition of the TBP intermediate is much faster in the cyclic than in the acyclic case; *i.e.*, $k_{(17)\rightarrow(18)} \gg k_{(11)\rightarrow(14)}$.

3. The reaction of the acyclic ester *(8)→(14)* is much slower than that of the cyclic one *(15)→(18)* because in the former, Reaction 5.6C, the isomerization *(9)→(11)* is a necessary step, while such a step is not required in the latter, Reaction 5.7C, to realize the conversion *(15)→(18)*. In the acyclic case, either $k_{(11)\rightarrow(14)} \gg k_{(11)\rightarrow(9)}$, or $k_{(9)\rightarrow(8)} \gg k_{(9)\rightarrow(11)}$, while in the cyclic case, $k_{(17)\rightarrow(15)}$ and $k_{(15)\rightarrow(17)}$ do not differ appreciably.

It is not reasonable to attribute[5,8] the faster rate of hydrolysis with ring-opening, *(15)→(18)*, *vs.* the hydrolysis of trimethyl phosphate, *(8)→(14)*, to a particular feature of the substrates *(8)* and *(15)*, *on purely kinetic grounds*, unless it is clearly established which of these three factors is responsible for the observed rate differences. Even if ring strain[5,8] exists in the cyclic phosphate *(15)*, the kinetic data do not justify the conclusion that *(15)* hydrolyses faster than *(18)* due to ring strain in phosphate ester, because the strain affects factors *(1)*, *(2)*, and *(3)* in different ways.

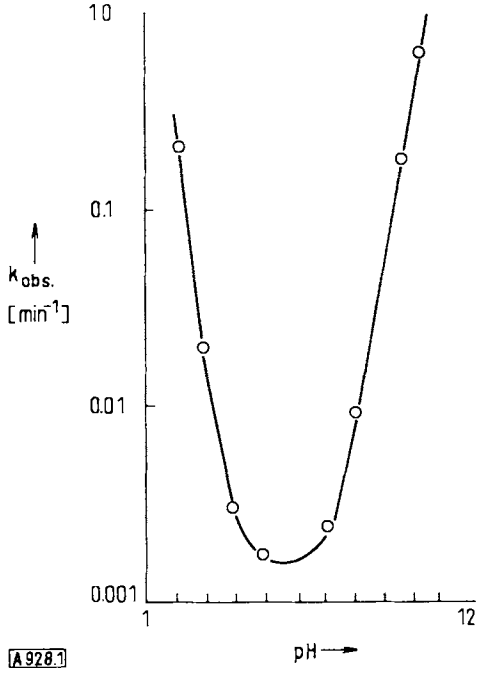


Fig. 1. The pH dependence of methyl ethylene phosphate hydrolysis rates at 25 °C.

We turn now to the observed[8e] pH dependence of the rate constants for the hydrolysis of methyl ethylene phosphate *(15)* (Reaction 5.7A). This phenomenon is depicted in Figure 1.

The observed rate constants can be expressed[8e] by Equation (5.7 m), while the various terms correspond to the different *mechanisms* discussed above.

$$k_{obs.} = k_{H^{\oplus},obs.}[H^{\oplus}] + k_{W,obs.} + k_{OH^{\ominus},obs.}[OH^{\ominus}] + k_{2OH^{\ominus},obs.}[OH^{\ominus}]^2 \quad (5.7\,m)$$

(at 25 °C: $k_{H^{\oplus},obs.} = 0.35\ M^{-1}s^{-1}$; $k_{W,obs.} = 2.3 \times 10^{-5}\,s^{-1}$; $k_{OH^{\ominus},obs.} = 64\ M^{-1}s^{-1}$)

The ratio of exocyclic hydrolysis *(15)→(24)* *vs.* ring opening *(15)→(18)* does not correlate in any simple manner with the pH-rate profile. Rather, the ratio is a complex function of the pH (cf. Figure 2)[8e].

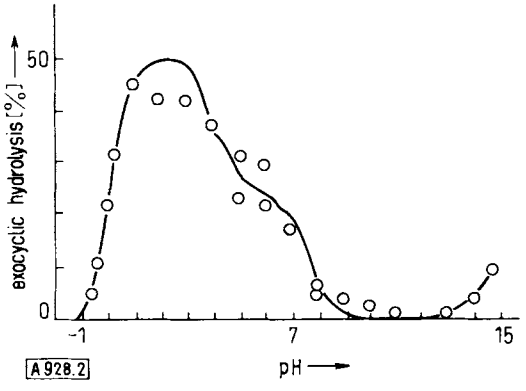


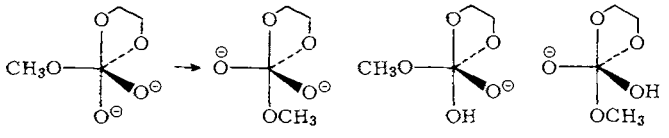
Fig. 2. Methyl ethylene phosphate hydrolysis pH-product profile.

In acidic solution the hydrolysis of methyl ethylene phosphate takes place according to the mechanism which is given by the general formulation of Reaction 5.2 and by the more detailed picture of Reaction 5.7A. The falloff of the exocyclic hydrolysis in strong acid[8e] can be attributed to the fact that the rate of hydrolysis with ring opening (*(15)→(17)→(18)*, after suitable protonation) is proportional to the proton concentration, whereas the rate of permutational isomerization of the oxyphosphorane intermediate when required for exocyclic hydrolysis (*(15)→(17)→(21)→(24)*, after suitable protonation) is independent of the acidity of the medium. Therefore, at high acidities, the rate of exocyclic hydrolysis is determined by the TR processes and fails to keep pace with ring opening; consequently, the yield of exocyclic products falls towards zero.

In the region of pH = 4 – 11 the curve of Figure 2 can be expressed in terms of the fraction of reaction that occurs *via* acid and hydroxide ion catalysis, as well as the water reaction, assuming[8e] that the acid catalyzed reaction gives 50%, the water reaction 25% (the corresponding hydrolysis in aprotic solvents proceeds with 100% ring retention (see Section 6)), and the hydroxide ion reaction 0% exocyclic hydrolysis. In strong alkali (pH > 12), the $[OH^{\ominus}]^2$ dependent reaction also takes place and the fraction of exocyclic hydrolysis rises in an approximately linear fashion with the hydroxide ion concentration to about 15% exocyclic cleavage in 10 M alkali[8e]. It was suggested[8e] that this behavior resulted from the formation of the dianion *(25a)* in strong alkali, assuming

that the concentration of the dianion *(25a)* is proportional to $[OH^{\ominus}]^2$. The dianion *(25a)* is then said to undergo the BPR process to form the new dianion *(25b)*, which should be more stable than *(25a)* according to the modified polarity rule. Dianion *(25b)* can account for the exocyclic hydrolysis to *(24)*. The apical hydroxy groups of hydroxyphosphoranes are very weakly acidic[2], and it seems that this acidity should be even weaker when the first anion has already been formed and has its oxide group in the equatorial position (cf. *(17)*). If the dianion *(25b)* is to be invoked at all, it would be logical to first isomerize the monoanion *(17)* to *(21)* by the TR process and then ionize the somewhat stronger equatorial OH to give the dianion *(25b)*. However, neither of these alternatives is very plausible. The hydrolysis of methyl ethylene phosphate in a strong alkaline medium probably proceeds *via* hexacoordinate species as described in Reaction 5.3. Although it was mentioned[8e], this possibility, was not pursued further. The rate of hydrolysis *via* hexacoordinate species would be proportional to $[OH^{\ominus}]^2$ in agreement with the experiments; this mechanism also predicts approxi-

Reaction 5.7E



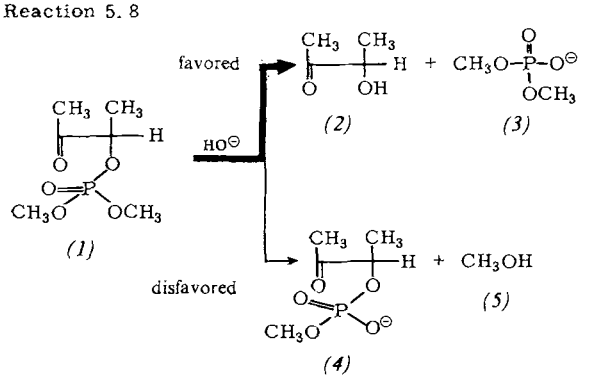
(25a) *(25b)* *(17)* *(21)*

mately equal yields of the products of exocyclic and of ring-opening hydrolyses. The mechanism *via* hexacoordinate species is also in line with the known[21] nucleophilic substitutions of oxyphosphoranes by alcohols catalyzed by bases; see Section 2.

5.2. The Fast Alkaline Hydrolyses of Dimethyl Acetoin Phosphate and Methyl Acetoin Methylphosphonate

The hydrolysis of dimethyl acetoin phosphate *(1)*, Reaction 5.8, at pH = 7.7 – 8.2, is extremely fast relative to the hydrolysis of trimethyl phosphate under comparable

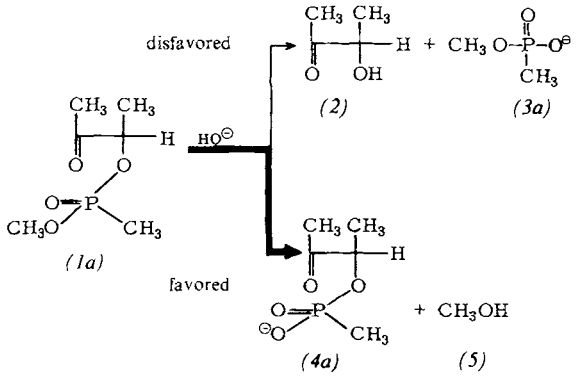
Reaction 5.8



conditions[11]. The products are mainly acetoin *(2)* and dimethyl phosphate *(3)*; ("acetoin displacement"). Very little[12] (*ca.* 3–4%) methanol *(5)* and methyl acetoin phosphate *(4)* are formed; ("methanol displacement").

The comparable hydrolysis of methyl acetoin methylphosphonate[12] *(1a)*, Reaction 5.9, is 200 times slower than that of the phosphate *(1)*, and gives mainly methanol *(5)* and acetoin methylphosphonate *(4a)* (*ca.* 95%).

Reaction 5.9



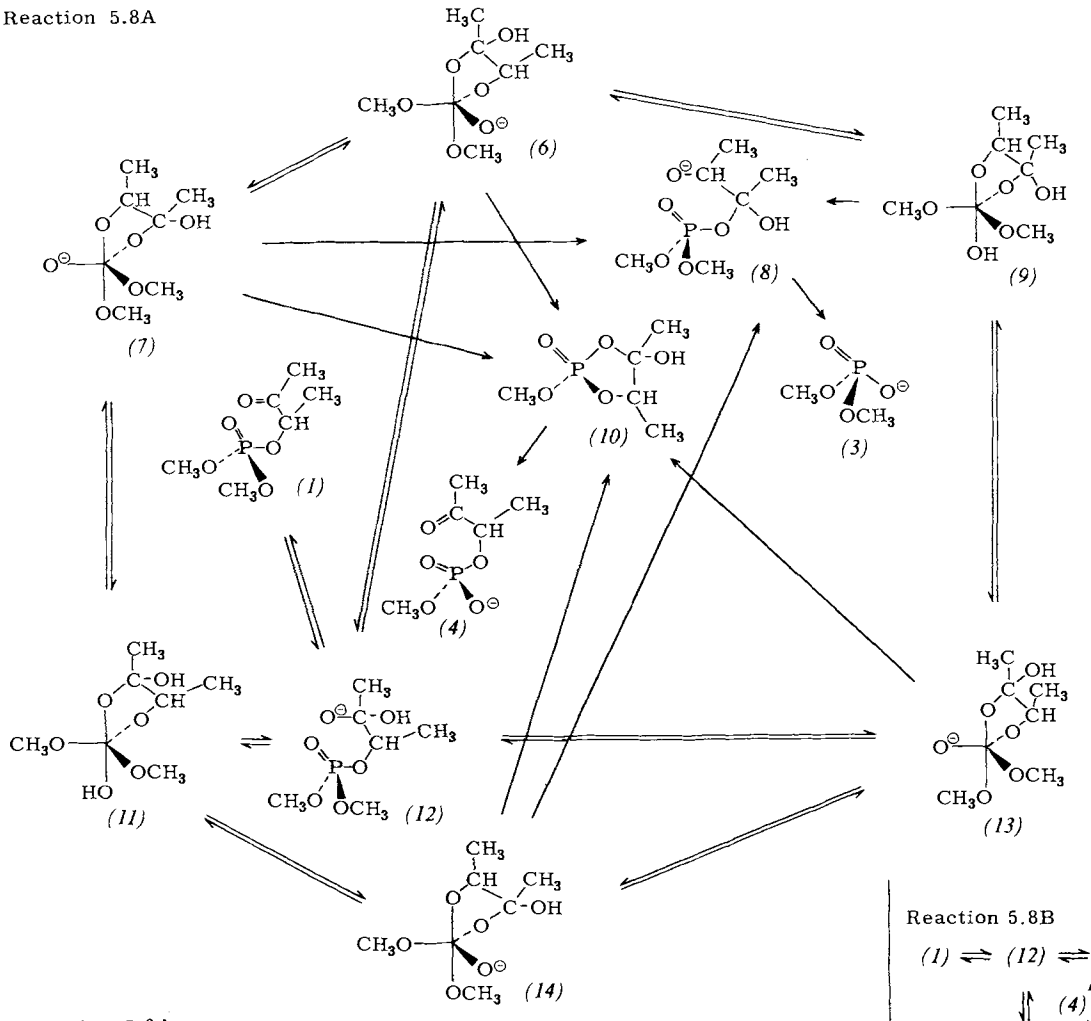
The rates[12] of the methanol-displacement reactions are of the same order of magnitude in both cases: $k_{(1)\rightarrow(4),\,obs.} \approx k_{(1a)\rightarrow(4a),\,obs.}$. However, the rate[12] of the acetoin displacement is about 600 times faster in the phosphate, *(1)*→*(2)*, than in the phosphonate *(1a)*→*(2)* ($k_{(1)\rightarrow(3),\,obs.} \gg k_{(1a)\rightarrow(3a),\,obs.}$). A available data strongly favor a mechanism involving participation of the carbonyl function in the formation of oxyphosphorane intermediates[11]. However, the data do not mandatorily eliminate mechanisms which involve the enol forms of *(1)* and *(1a)*, or the cleavage of the C_α—O bond. The reaction mechanisms 5.8A and 5.9A which are based upon oxyphosphorane intermediates whose premises are outlined in Section 4 account nicely for the observed data concerning Reactions 5.8 and 5.9. The essential differences between these two is that *the TBP intermediates (13) and (7) (Reaction 5.8A) have no counterpart in the phosphonate case (Reaction 5.9A) because in the latter case the TBP would have to carry apical* P—CH_3 *bonds in violation of the modified polarity rule.* This violation of the modified polarity rule renders the corresponding reaction pathways non-competitive relative to other allowed pathways in the phosphonate case.

To arrive at manageable kinetic expressions, Reaction 5.8A for the phosphate is simplified to Reaction 5.8B, and Reaction 5.9A for the phosphonate is simplified to Reactions 5.9B, by taking into consideration only the most probable of the competing parallel reactions, and by combining some steps in the reaction sequences.

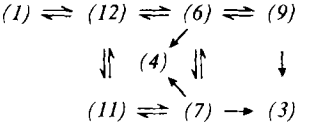
Note that *(7a)* and *(13a)* cannot be generated.

The kinetic expressions for the phosphate hydrolysis according to Reaction 5.8B are given in Equations (5.8a) to (5.8h). The corresponding expressions for phosphonate hydrolysis according to Reaction 5.9B are given in Equations (5.9a) to (5.9d). The rate ratios for methanol displacement (*i.e.*, formation of *(4)* or of *(4a)*) relative to acetoin-

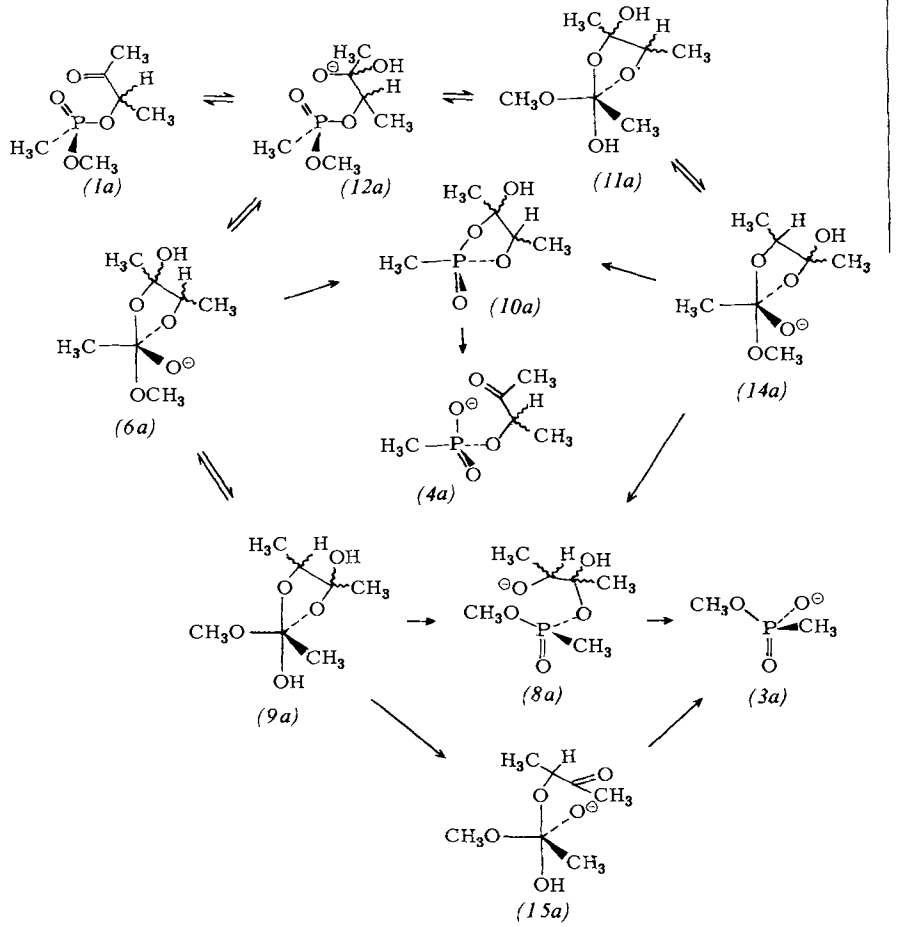
Reaction 5.8A



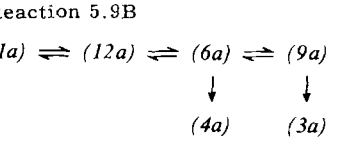
Reaction 5.8B



Reaction 5.9A



Reaction 5.9B



displacement (*i.e.*, formation of *(3)* or of *(3a)*) for the phosphate and the phosphonate, respectively, are shown in Equation (5.8c) and Equation (5.9d).

$$\frac{d[(3)]}{dt} = \frac{[OH^{\ominus}][(1)]k_{(1)\rightarrow(12)}\cdot k_{(12)\rightarrow(11)}\cdot K[k_{(7)\rightarrow(3)}\cdot L + k_{(6)\rightarrow(9)}\cdot k_{(9)\rightarrow(3)}(k_{(9)\rightarrow(3)}+k_{(9)\rightarrow(6)})^{-1}M]}{LO-MN} \quad (5.8a)$$

$$\frac{d[(4)]}{dt} = \frac{[OH^{\ominus}][(1)]k_{(1)\rightarrow(12)}\cdot k_{(12)\rightarrow(11)}\cdot K[k_{(7)\rightarrow(4)}\cdot L + k_{(6)\rightarrow(4)}M]}{LO-MN} \quad (5.8b)$$

Methanol displacement/acetoin displacement:

$$\frac{d[(4)]}{dt}\Big/\frac{d[(3)]}{dt} = (k_{(7)\rightarrow(4)}\cdot L + k_{(6)\rightarrow(4)}\cdot M)[k_{(7)\rightarrow(3)}L + k_{(6)\rightarrow(9)}k_{(9)\rightarrow(3)}(k_{(9)\rightarrow(3)}+k_{(9)\rightarrow(6)})^{-1}M]^{-1} \quad (5.8c)$$

with

$$K = [(k_{(11)\rightarrow(7)}+k_{(11)\rightarrow(12)})(k_{(12)\rightarrow(1)}+k_{(12)\rightarrow(6)}+k_{(12)\rightarrow(11)}) - k_{(11)\rightarrow(12)}k_{(12)\rightarrow(11)}]^{-1} \quad (5.8d)$$

$$L = k_{(6)\rightarrow(7)}\cdot k^{-1}_{(11)\rightarrow(7)} - k_{(11)\rightarrow(12)}\cdot k^{-1}_{(12)\rightarrow(6)}(k_{(11)\rightarrow(7)} + k_{(11)\rightarrow(12)})^{-1}(k_{(6)\rightarrow(1)}+k_{(6)\rightarrow(7)}+k_{(6)\rightarrow(9)}+k_{(6)\rightarrow(12)}) + k_{(6)\rightarrow(9)}\cdot k_{(9)\rightarrow(6)}\cdot k^{-1}_{(12)\rightarrow(6)} \times k_{(12)\rightarrow(11)}(k_{(9)\rightarrow(3)}+k_{(9\rightarrow6)})^{-1}(k_{(11)\rightarrow(7)}+k_{(11)\rightarrow(12)})^{-1} \quad (5.8e)$$

$$M = k^{-1}_{(11)\rightarrow(7)}(k_{(7)\rightarrow(3)} - k_{(7)\rightarrow(4)} + k_{(7)\rightarrow(6)} + k_{(7)\rightarrow(11)}) + k^{-1}_{(12)\rightarrow(6)}(k_{(7)\rightarrow(11)}\cdot k_{(12)\rightarrow(6)} - k_{(7)\rightarrow(6)}\cdot k_{(12)\rightarrow(11)}) \times (k_{(11)\rightarrow(7)}+k_{(11)\rightarrow(12)})^{-1} \quad (5.8f)$$

$$N = k_{(6)\rightarrow(7)}\cdot k^{-1}_{(1)\rightarrow(7)} + k_{(6)\rightarrow(11)}\cdot k_{(12)\rightarrow(11)}K \quad (5.8g)$$

$$O = k^{-1}_{(11)\rightarrow(7)}(k_{(7)\rightarrow(3)}+k_{(7)\rightarrow(4)}+k_{(7)\rightarrow(6)}+k_{(7)\rightarrow(11)}) - k_{(7)\rightarrow(11)}\cdot K(k_{(12)\rightarrow(1)}+k_{(12)\rightarrow(6)}+k_{(12)\rightarrow(11)}) \quad (5.8h)$$

$$\frac{d[(4a)]}{dt} = [(1a)][OH^{\ominus}]\cdot k_{(6a)\rightarrow(4a)}\cdot P \quad (5.9a)$$

$$\frac{d[(3a)]}{dt} = [(1a)][OH^{\ominus}]\cdot k_{(6a)\rightarrow(9a)} \times k_{(9a)\rightarrow(3a)}(k_{(6a)\rightarrow(9a)}+k_{(9a)\rightarrow(3a)})^{-1}P \quad (5.9b)$$

$$P = [k^{-1}_{(1a)\rightarrow(12a)}\cdot k^{-1}_{(12a)\rightarrow(6a)}(k_{(12a)\rightarrow(1a)}+k_{(12a)\rightarrow(6a)})(k_{(6a)\rightarrow(12a)} + k_{(6a)\rightarrow(4a)}+k_{(6a)\rightarrow(9a)}) - k_{(12a)\rightarrow(6a)}\cdot k^{-1}_{(6a)\rightarrow(12a)} + k^{-1}_{(6a)\rightarrow(9a)} \times k^{-1}_{(9a)\rightarrow(12a)}(k_{(12a)\rightarrow(1a)}+k_{(12a)\rightarrow(6a)})(k_{(9a)\rightarrow(6a)}+k_{(9a)\rightarrow(3a)})]^{-1} \quad (5.9c)$$

Methanol displacement/acetoin displacement:

$$\frac{d[(4a)]}{dt}\Big/\frac{d[(3a)]}{dt} = k_{(6a)\rightarrow(4a)}\cdot k^{-1}_{(6a)\rightarrow(9a)}\cdot k^{-1}_{(9a)\rightarrow(3a)} \times (k_{(9a)\rightarrow(6a)}+k_{(9a)\rightarrow(3a)}) \quad (5.9d)$$

The observed fact that

$$k_{\text{obs. }(1)\rightarrow(4)} \ll k_{\text{obs. }(1)\rightarrow(3)} \quad (k_{\text{Methanol}} \ll k_{\text{Acetoin}}) \quad (5.8i)$$

corresponds to

$$k_{(7)\rightarrow(4)}\cdot L + k_{(6)\rightarrow(4)}\cdot M \ll k_{(7)\rightarrow(3)}\cdot L + k_{(6)\rightarrow(9)}\cdot k_{(9)\rightarrow(3)} \times (k_{(9)\rightarrow(3)}+k_{(9)\rightarrow(6)})^{-1}M \quad (5.8j)$$

which leads to:

$$k_{(6)\rightarrow(4)} \ll k_{(6)\rightarrow(9)}\cdot k_{(9)\rightarrow(3)}(k_{(9)\rightarrow(3)}+k_{(9)\rightarrow(6)})^{-1} \quad (5.8k)$$

when

$$L \ll M \quad (5.8l)$$

with the additional assumption that

$$k_{(9)\rightarrow(3)} \gg k_{(9)\rightarrow(6)} \quad (5.8m)$$

Equation (5.8k) implies that:

$$k_{(6)\rightarrow(4)} \ll k_{(6)\rightarrow(9)} \quad (k_{\text{collapse with ring retention}} \ll k_{TR}) \quad (5.8n)$$

i.e., the permutation isomerization *(6)→(9)* is much faster than the collapse of the oxyphosphorane *(6)*. On the other hand, from Equation (5.8j) it follows that:

$$k_{(7)\rightarrow(4)} \ll k_{(7)\rightarrow(3)} \quad \begin{matrix}(\text{collapse with ring retention} \\ \ll \text{collapse with ring opening})\end{matrix} \quad (5.8o)$$

i.e., the collapse of the oxyphosphorane *(7)* with ring opening to *(8)* and thence to *(3)* is much faster than its collapse with ring retention to *(10)* and thence to *(4)*, when

$$M \ll L \quad (5.8p)$$

From Equation (5.9d) and:

$$k_{\text{obs. }(1a)\rightarrow(4a)} \gg k_{\text{obs. }(1a)\rightarrow(3a)} \quad (k_{\text{obs. methanol displacement}} \gg k_{\text{obs. acetoin displacement}}) \quad (5.9e)$$

it can be concluded that

$$(k_{(9a)\rightarrow(6a)}+k_{(9a\rightarrow(3a)})\,k_{(6a)\rightarrow(4a)} \gg k_{(6a)\rightarrow(9a)}\cdot k_{(9a)\rightarrow(3a)} \quad (5.9f)$$

which, with the assumption

$$k_{(9a)\rightarrow(6a)} \ll k_{(9a)\rightarrow(3a)} \quad (k_{TR} \ll k_{\text{collapse with ring opening}}) \quad (5.9g)$$

implies

$$k_{(6a)\rightarrow(4a)} \ll k_{(6a)\rightarrow(9a)} \quad (k_{\text{collapse with ring retention}} \ll k_{TR}) \quad (5.9h)$$

Further, since *(1)→(4)* and *(1a)→(4a)* are similar processes with similar observed rates, the *faster overall hydrolysis of (1) over that of (1a) is primarily due to the fact that the positional exchange processes of Reaction 5.8A which led to (3) have no counterparts in Reaction 5.9A.* According to Equations (5.8a), (5.8b) and (5.9a), (5.9b), the relatively high rates of alkaline hydrolysis of *(1)* and *(1a)* are mainly due to the fast formations of the intermediates *(12)* and *(12a)* from *(1)* and *(1a)* and also to the high rates of the processes *(12)→(6)*, *(11)→(7)*, *(9)→(3)*, and *(6a)→(4a)*, respectively.

The relatively fast formation of the oxyphosphorane intermediates from *(12)* and *(12a)* is due to the fact that those

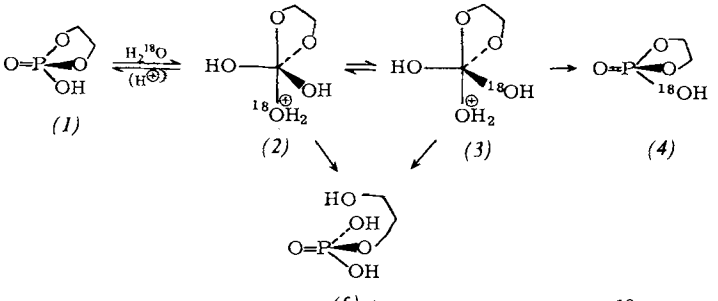
processes are first order reactions which lead to *unstrained five-membered rings*, providing a further argument against the assumption of the relief of five-membered ring strain[5,8] being responsible for the rapid hydrolyses of ethylene phosphates and related compounds. In fact, the enhancement of the rate can be said to be due to the tendency that exists for the formation of the five-membered ring in a TBP pentacoordinate phosphorane.

One of the consequences of the kinetic analysis presented above is that in the case of the reactions of oxyphosphoranes derived from dimethyl phosphoacetoin, the collapse of a phosphorane with ring opening is kinetically favored over the collapse of a phosphorane with ring retention. This is in apparent contradiction to the principle enunciated in Section 4.5 to the effect that collapse of the cyclic oxyphosphorane with ring retention is favored over collapse of a phosphorane with ring opening. However, it should be noted that formula *(9a)* of Reaction 5.9A is an unusual type of oxyphosphorane, since it has a hemiacetal function at the quasiequatorial carbon. We suggest therefore that in such cases the rupture of the hemiacetal C—O bond to the acyclic oxyphosphorane *(15a)* is favored over the rupture of the apical P—O bond of *(9a)* with the formation of *(8a)*. This interpretation retains the generality of the statement given in Section 4.5 for the non-hemiacetal oxyphosphorane.

5.3. Acid Hydrolysis and ^{18}O-Exchange of Ethylene Phosphate

One of the earliest and most significant experiments bearing on the mechanism of hydrolysis of phosphate esters is the observation of the oxygen-exchange that accompanies the acid hydrolysis of the five-membered cyclic ethylene phosphate *(1)*[5,8a], Reaction 5.10. The permutational isomerization *(2)*⇄*(3)* is simplified in this representation and probably involves deprotonation, isomerization by the TR mechanism, and reprotonation of the OH at the apical position which is more capable of sustaining the most electronegative ligand[2].

Reaction 5.10



(1) *(2)* *(3)* *(4)*

(5) (partially labeled with ^{18}O)

This experiment strongly supports the hypothesis that oxyphosphoranes are formed in these hydrolyses, and that the TBP pentacoordinate intermediates are capable of undergoing permutational isomerizations. However, one must reexamine the previous interpretation[5,8a] of the kinetic data in the light of concepts presented in this Review. Concepts in question are those pertaining to the relative rates of the permutational isomerization steps and to the mechanism, *i.e.*, BPR or TR, by which this type of isomerization takes place in *cyclic* oxyphosphorane derivatives.

The picture of Reaction 5.10 leads to the kinetic expressions given in Equations (5.10a) to (5.10c):

$$\frac{d[(4)]}{dt} = [(1)][H^{\oplus}]\cdot k_{(3)\rightarrow(4)}\cdot J \qquad (5.10a)$$

$$\frac{d[(5)]}{dt} = [(1)][H^{\oplus}][k_{(2)\rightarrow(5)}\, k^{-1}_{(2)\rightarrow(3)}(k_{(3)\rightarrow(2)}+k_{(3)\rightarrow(4)} + k_{(3)\rightarrow(5)})+k_{(3)\rightarrow(5)}]\cdot J \qquad (5.10b)$$

$$J = k_{(1)\rightarrow(2)}k_{(2)\rightarrow(3)}[(k_{(2)\rightarrow(1)}+k_{(2)\rightarrow(3)}+k_{(2)\rightarrow(5)})(k_{(3)\rightarrow(2)} + k_{(3)\rightarrow(4)}+k_{(3)\rightarrow(5)})-k_{(3)\rightarrow(2)}k_{(2)\rightarrow(3)}]^{-1} \qquad (5.10c)$$

Making the assumptions that the permutational isomerizations *(2)*⇄*(3)* occur at the same rate in both directions, $k_{(2)\rightarrow(3)}=k_{(3)\rightarrow(2)}$, and that both analogous oxyphosphoranes *(2)* and *(3)* decompose with ring opening at the same rate, $k_{(2)\rightarrow(5)}=k_{(3)\rightarrow(5)}$ (deprotonations and reprotonations are neglected in these representations) one arrives at Equation (5.10d) for the ratio of the rates of hydrolysis *vs.* oxygen exchange:

$$\frac{d[(5)]}{dt}\Big/\frac{d[(4)]}{dt} = [k_{(2)\rightarrow(5)}\cdot k^{-1}_{(2)\rightarrow(3)}(k_{(3)\rightarrow(2)}+k_{(3)\rightarrow(4)}+k_{(3)\rightarrow(5)}) + k_{(3)\rightarrow(5)}]\cdot k^{-1}_{(3)\rightarrow(4)} \qquad (5.10d)$$

Two significantly different situations can now be envisioned. The first involves the hypothesis *that the permutational isomerization among the oxyphosphoranes is faster than their decomposition to tetracoordinate phosphates:* $k_{(2)\rightarrow(3)}$, $k_{(3)\rightarrow(2)} \gg k_{(2)\rightarrow(5)}$, $k_{(3)\rightarrow(4)}$, $k_{(3)\rightarrow(5)}$. Under this assumption, the experimentally observed ratio

$$\frac{d[(5)]}{dt}\Big/\frac{d[(4)]}{dt} = 5 \quad \text{(ratio of ring opening : ring retention)} \qquad (5.10e)$$

for the rates of hydrolysis *vs.* oxygen exchange leads to Equation (5.10f). In other words, the tendency of an oxyphosphorane to lose one mole of water (where the ring is retained) is 2.5 times less pronounced than its tendency to undergo ring opening.

$$k_{(3)\rightarrow(4)} = 0.4\, k_{(2)\rightarrow(5)} \quad (i.e., \text{the rate of collapse with ring retention} = 0.4 \times \text{rate of collapse with ring opening}) \qquad (5.10f)$$

The second situation involves the hypothesis that the *permutational isomerization of the oxyphosphoranes is slower than their decomposition to tetraccordinate phosphates:* $k_{(2)\rightarrow(3)}, k_{(3)\rightarrow(2)} \ll k_{(2)\rightarrow(5)}, k_{(3)\rightarrow(4)}, k_{(3)\rightarrow(5)}$. This type of hypothesis has been recently suggested by *Westheimer et al.*[8e]; in it, with $k_{(2)\rightarrow(5)}=k_{(3)\rightarrow(5)}=\alpha k_{(3)\rightarrow(4)}$, one should obtain Equation (5.10g). Since the assumption[8e] that isomerization is much slower than decomposition ($k_{(2)\rightarrow(3)} \ll k_{(2)\rightarrow(5)}$), Equation (5.10g) is hardly compatible with the values (Eq. 5.10e) observed for the ratio of the rates of hydrolysis *(1)*→*(5)* *vs.* oxygen exchange *(1)*→*(4)*. Therefore, this assumption is untenable

and $k_{(2)\rightarrow(3)}$, $k_{(3)\rightarrow(2)}$ must be of the same order of magnitude as $k_{(2)\rightarrow(5)}$, $k_{(3)\rightarrow(4)}$, or more likely, as stated above $k_{(2)\rightarrow(3)}, k_{(3)\rightarrow(2)} \gg k_{(2)\rightarrow(5)}, k_{(3)\rightarrow(4)}$.

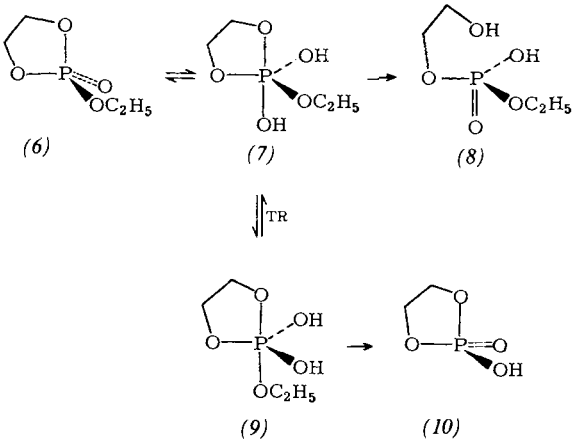
$$\frac{d[(5)]}{dt} \Big/ \frac{d[(4)]}{dt} = k_{(2)\rightarrow(5)}(1+\alpha)\cdot k^{-1}_{(2)\rightarrow(3)} \qquad (5.10g)$$

Again the slight tendency for an oxyphosphorane to collapse with ring opening instead of with ring retention is in apparent contradiction with the conclusion reached in Section 4.5. However, it should be noted that this principle refers to the loss of an alkoxyl group from an oxyphosphorane in both cases (*i.e.*, where the ring is retained and where the ring is opened). On the other hand, in Reaction 5.10 a water molecule is the leaving group in ring retention (*(3)→(4)*) while the alkoxy group is the leaving group in ring opening (*(3)→(5)*). We would suggest that the general tendency of oxyphosphoranes to undergo collapse with ring retention is offset to some extent by the higher leaving tendency of an alkoxy group, as compared with water. It is remarkable, in fact, that the ring opening is only 2.5 times greater than ring retention. It should also be emphasized that the acyclic oxyphosphorane *(15a)* of Reaction 5.9A has the option to collapse with the loss of alkoxide to give *(3a)* and acetoin or to collapse with the loss of hydroxide to give *(1a)*. This is another case of the collapse of an oxyphosphorane with loss of an alkoxide taking precedence over collapse with the loss of a hydroxide.

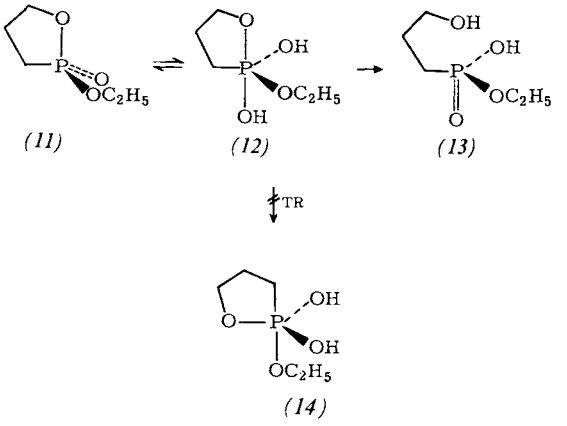
Finally, the relatively high rate of acid hydrolysis of ethylene phosphate *(1)→(5)*, Reaction 5.10, relative to the acid hydrolysis of dimethyl phosphate, $(CH_3O)_2P(O)OH$, can be interpreted by assuming that *the formation of the TBP intermediate is faster in the presence of a five-membered ring.* This is another example of the principle enunciated in Sections 2 and 4, namely, that there is a kinetic (as well as a thermodynamic) advantage in the conversion of a five-membered cyclic tetracoordinate phosphate into a five-membered cyclic pentacoordinate oxyphosphorane, for the reasons given in those Sections.

The relatively rapid permutational isomerization of the oxyphosphoranes *(2)⇄(3)*, Reaction 5.10, is understandable in the TR mechanism[2,29] using the ring as the pair of the pair-trio TR-combination.

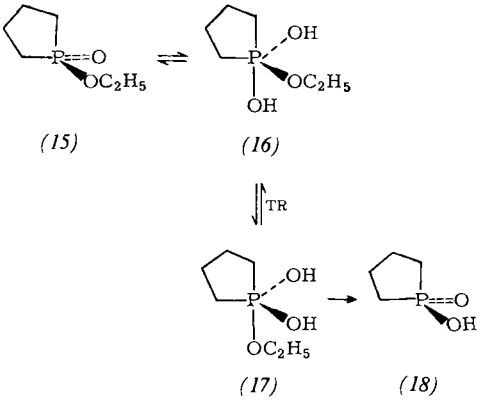
Reaction 5.11



Reaction 5.12



Reaction 5.13



5.4. Differences in the Hydrolytic Behavior of Cyclic Phosphate, Phosphonate, and Phosphinate Esters

Interpretation of behavior differences in the hydrolyses of cyclic phosphate, phosphonate and phosphinate esters where phosphorus lies incorporated in a five-membered ring[8c,e,f] follows directly from the previously mentioned TR rule for cyclic phosphoranes (see Section 4.10; 8).

In contrast to the corresponding cyclic phosphate *(6)* (Reaction 5.11) which leads to *(8)* and *(10)*, the fast hydrolysis of the cyclic phosphonate *(11)* (Reaction 5.12) proceeds exclusively with ring opening forming *(13)*. The oxyphosphorane intermediate *(12)* is incapable of rearrangement by a single TR process with the ring as the pair, since this would generate *(14)* with an energetically disfavored apical P—C bond. A $(TR)^2$ process which may lead to exocyclic hydrolysis is also disfavored for reasons given in Ref.[2].

The acid hydrolysis of cyclic phosphate *(6)* corresponds mechanistically to the analogous preceding case (Reaction 5.10).

The cyclic phosphinate ester *(15)* behaves as expected. Now, hydrolysis is possible only after the TR *(16)→(17)* in which the ring acts as the pair. In both *(16)* and *(17)* there is an apical P—C bond and hence the energies of the two TBP are of the same order of magnitude and the TR *(16)→(17)* is thermodynamically permissible. The relatively slow observed rate of hydrolysis of *(15)* can result from either one of the following factors or their combination (see Equations (5.13a) to (5.13c)): 1. The TBP intermediate

(16) is relatively energy rich due to the apical carbon (in contrast to *(7)* and *(12)*); this would make step *(15)*→*(16)* slow. 2. The TR barrier of *(16)*→*(17)* is expected to be relatively high since the two P—CH_2 groups interfere sterically with the P—O moiety. In the phosphate case, *(7)*→*(9)*, this type of interference is absent. Thus, the relatively slow rate of hydrolysis of the cyclic phosphinate *(16)* to *(18)* is accounted for.

$$k_{\text{hydrol, obs.}} = k_{(15)\rightarrow(16)} \cdot k_{(17)\rightarrow(18)} [(k_{(16)\rightarrow(15)} + k_{(16)\rightarrow(17)})(k_{(17)\rightarrow(16)} + k_{(17)\rightarrow(18)}) k^{-1}_{(16)\rightarrow(17)} - k_{(17)\rightarrow(16)}]^{-1} \quad (5.13a)$$

For the extremes, Equation (5.13b) follows with the assumption
$k_{(16)\rightarrow(17)}, k_{(17)\rightarrow(16)} \gg k_{(16)\rightarrow(15)}$:

$$k_{\text{hydrol, obs.}} = k_{(15)\rightarrow(16)} \quad (5.13b)$$

and Equation (5.13c) with the assumptions $k_{(16)\rightarrow(17)}$, $k_{(17)\rightarrow(16)} \gg k_{(16)\rightarrow(15)}$, $k_{(17)\rightarrow(18)}$, and $k_{(15)\rightarrow(16)} \approx k_{(16)\rightarrow(15)}$

$$k_{\text{hydrol, obs.}} = k_{(16)\rightarrow(17)} \quad (5.13c)$$

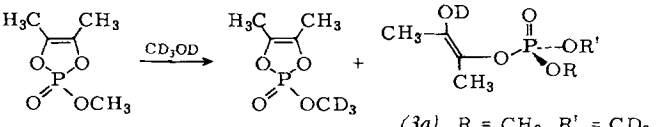
6. Hydrolyses and Rearrangements of Phosphate Esters in Aprotic Solvents and in Neutral Aqueous Solutions

In neutral media where oxyphosphorane intermediates exist neither in protonated nor anionic form, their collapse by departure of an apical ligand is accompanied by charge separation (see Section 4.7), unless rapid proton transfer from hydrogen bonded water molecules takes place. Hence it can be predicted that the lifetime of oxyphosphorane intermediates in neutral media is much longer than in acidic or alkaline solutions, and positional exchange is more likely to occur.

According to the pH-rate profile[8e] for the hydrolysis of methyl ethylene phosphate (see Section 5.1), the acid catalyzed reaction gives 50% exocyclic hydrolysis; the ring-retention process falls off to 25% for the water reaction and to 0% for the hydroxide-ion reaction. In the hydrolysis of five-membered cyclic phosphate esters in aprotic solvents with limited amounts of water[9a,61c,d,h], *there is always a remarkable tendency for exocyclic hydrolysis, and in some cases, nearly complete retention of the ring could be demonstrated*[9a,61c,d,h]. To detect this tendency toward ring retention, one must avoid the secondary reactions of the products that are formed in the first stage. It is not quite clear at this time why the cyclic oxyphosphorane intermediates in these reactions manifest such preference for collapse with exocyclic apical departure of, *e.g.*, methanol leading to hydrolysis with ring retention. Presumably the corresponding transition state is less strained than the transition state for ring opening.

The enediol cyclophosphate *(1)*, Reaction 6.1, reacts with nucleophiles in aprotic solvents at an extraordinarily rapid rate[61c,h]. The approximate half-life of the reaction with one mol. equiv. of methanol in 0.3 M CCl_4 solution amounts to one minute at 20 °C[61h]. Methanol enters and leaves the molecule with retention of the ring; this exchange is followed by the slower rupture of the ring, as can be shown by the use of CD_3OD: *(1)*→*(2)*+*(3)*. Highly selective nucleic acid syntheses seem possible employing reactions of a type which is represented by this model[*].

Reaction 6.1[61c,h]

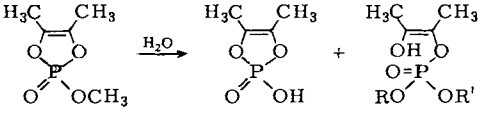


(1) *(2)*

(3a), R = CH_3, R' = CD_3
(3b), R = R' = CH_3
(3c), R = R' = CD_3

The addition of one mol. equiv. of water to a 0.6 M benzene solution of *(1)*, Reaction 6.2, gives within seconds the cyclic phosphodiester *(4)* and methanol. Subsequent reaction of the methanol thus formed with the unreacted cyclic triester *(1)* and with the cyclic diester *(4)* yield respectively the open phosphotriester *(5a)* and phosphodiester *(5b)*. There is also formed some open phosphomonoester *(5c)* which must have resulted from the reaction of water with the cyclic diester *(4)*[61h].

Reaction 6.2[61h]

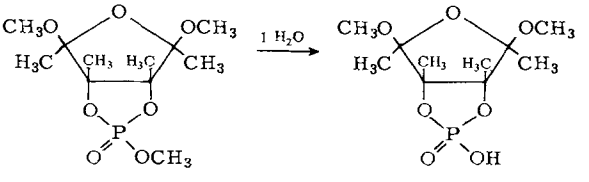


(1) *(4)*

(5a), R = R' = CH_3
(5b), R = CH_3, R' = H
(5c), R = R' = H

The furanose-2,3-cyclophosphotriester *(6)*, Reaction 6.3, undergoes rapid hydrolysis with *ca.* 100% ring retention in aprotic solvents[9a].

Reaction 6.3[9a]



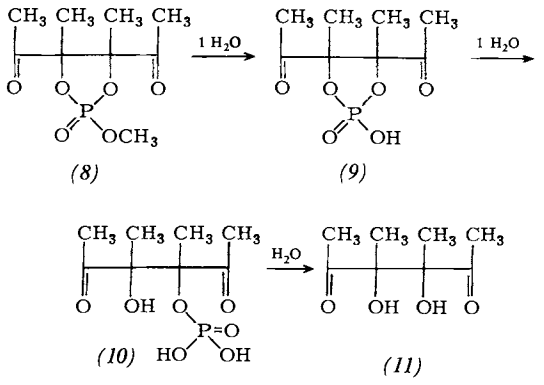
(6) *(7)*

Cyclic phosphotriesters derived from α,β-dihydroxy-γ-diketones *(8)*, Reaction 6.4, undergo hydrolysis, with *ca.* 100% ring retention *(8)*→*(9)*[9a,61]. Further hydrolytic cleavage of the ring is also rapid and gives the monoester *(10)*. The latter loses phosphoric acid quite rapidly, because the phosphate is activated by both adjacent functions, the carbonyl and the glycol-OH, *(10)*→*(11)* (see Section 5.2).

Cyclic phosphotriesters derived from α,β-dihydroxy-monoketones *(12)*, Reaction 6.5, illustrate nicely the relative activating effects of the carbonyl group and of the glycol-

[*] See also: *S. Glaser, F. Ramirez, P. Stern, P. D. Gillespie*, and *I. Ugi*, Angew. Chem. *85*, 39 (1973); Angew. Chem. internat. Edit. *12*, 66 (1973).

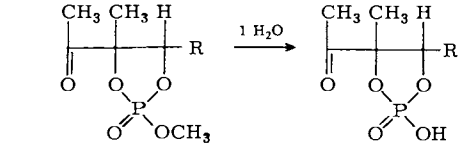
Reaction 6.4[9a,61c]



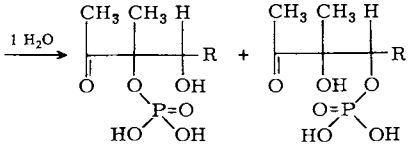
(8) (9) (10) (11)

OH group on adjacent phosphate esters[61d]. The first hydrolysis product is the cyclic phosphodiester *(13)* which undergoes subsequent hydrolytic cleavage to the α-phosphate *(14)* of the α,β-dihydroxyketone. The latter undergoes a relatively slow isomerization to the more stable β-phosphate *(15)*. The carbonyl group "pushes" the phosphate toward the β-ketol function, *(14)*→*(15)*.

Reaction 6.5[61d]



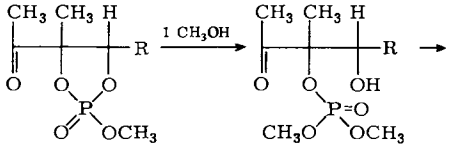
(12), R = CH_2CH_3, $CH{=}CH_2$ *(13)*



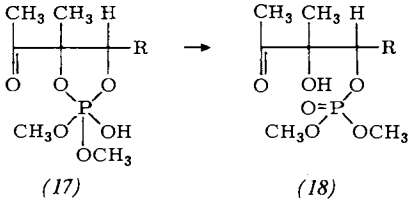
(14) *(15)*

The reactions of the α,β-dihydroxyketone-phosphotriesters *(12)*, Reaction 6.6, with methanol are very fast and give the α-phosphotriesters *(16)*. The product *(16)* undergoes an extremely rapid isomerization to the β-phosphotriester *(18)*. This isomerization is much faster than that of the monoester *(14)*.

Reaction 6.6[61d,f]



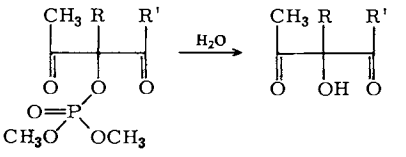
(12) *(16)*



(17) *(18)*

A phosphate ester flanked by two carbonyl groups, as in *(19)*, Reaction 6.7, represents a condition of extraordinary hydrolytic instability. This is true for phosphate esters of α-hydroxy-β-diketones *(19a)* and *(19b)*, α-hydroxy-β-ketoesters *(19c)*, and α-hydroxy-β-ketoamides *(19d)*, with and without α-hydrogens. The most reactive example is that of the phosphotriester *(19b)*, which loses its phosphate within minutes when treated with one mol. equiv. of water in ether solution at 0 °C[61e].

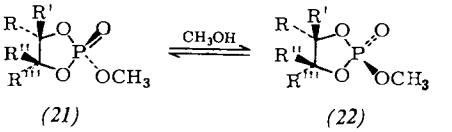
Reaction 6.7[61b,e]



(19a), R = R' = CH_3 *(20)*
(19b), R = CH_3, R' = CF_3
(19c), R = CH_3, R' = OCH_3
(19d), R = H, R' = NHR''

Diastereomeric five-membered cyclophosphotriesters such as *(21)* and *(22)*, Reaction 6.8, which differ by the configuration at the phosphorus, undergo rapid diastereomerization by inversion at the P-center under the catalytic influence of methanol[9b]. Permutational isomerization of the hypothetical oxyphosphorane intermediates by the TR with the ring as the pair accounts for these observations.

Reaction 6.8[9b]



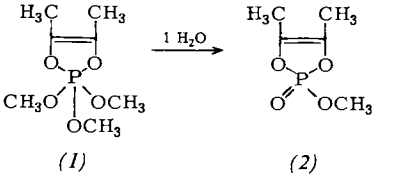
(21) *(22)*

7. Hydrolysis of Isolable Cyclic Oxyphosphoranes in Aprotic Solvents

The concept that transient oxyphosphoranes are formed in the hydrolyses of phosphate esters and related reactions, and the ideas presented in Sections 2 and 4 relative to the role of five-membered rings in those reactions, are supported by the behavior of the *isolable*, relatively stable, five-membered cyclic oxyphosphoranes toward water.

The reaction of one mol. equiv. of water with the five-membered cyclic unsaturated oxyphosphorane, Reaction 7.1, in benzene solution at 0 °C gives two mol. equivs. of methanol and the enediol cyclophosphate *(2)*.

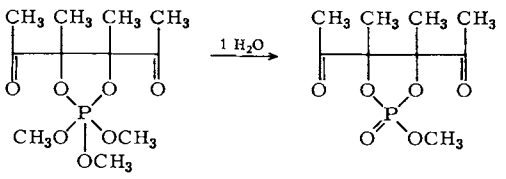
Reaction 7.1[21,61a,c]



(1) *(2)*

The oxyphosphorane *(3)*, Reaction 7.2, derived from the addition of two moles of diacetyl to one mole of trimethyl phosphite gives cyclic phosphotriesters *(4)* upon treatment with one mol. equiv. of water.

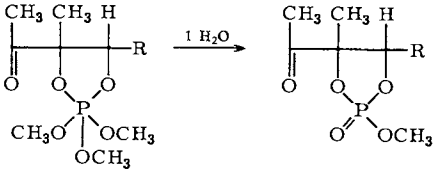
Reaction 7.2[9b,20a,b,d,61c]



(3) *(4)*

The oxyphosphoranes *(5)*, Reaction 7.3, which are made from the reaction of one mole each of diacetyl, an aldehyde, and trimethyl phosphite, show a marked tendency to undergo hydrolyses with ring-retention in aprotic media.

Reaction 7.3[61d,f]



(5) *(6)*

8. Conclusion

Nucleophilic displacement reactions of tetracoordinate phosphorus compounds, including biochemically important phosphoric acid derivatives, in general, proceed subject to the rules and concepts outlined above. These rules are primarily empirical, and based upon the known chemistry of the stable phosphorane derivatives and the experimental evidence which is available on nucleophilic displacement reactions of tetracoordinate phosphorus compounds. Moreover, some of these rules can be justified by quantum mechanical treatment[2] of the bonding properties of pentacoordinate phosphorus and its ligand sets. The latter includes the analysis of polytopal reorganization mechanisms based upon the subclasses of the symmetric permutation groups S_n[*] with respect to the skeletal symmetry subgroups[2]. The concepts presented in this and in the preceding communication[2] permit a consistent and unified treatment of an essential aspect of phosphorus chemistry. Indeed, it is possible at times to make detailed predictions of the relative rates and of the outcome of many reactions of phosphorus compounds.

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[*] *Note added in proof:* In this context the reader should recall the use of the structure of the symmetric group S_5 for the classification of the rearrangements of pentacoordinate molecules, as discussed in a preceding communication of this series [2].

The permutations belonging to the symmetric group S_5 correspond to the rearrangements of pentacoordinate molecules and are the *isomerizers* of pentacoordinate molecules [2].

Definitions for the terms arising from the treatment of the problem given in ref. [2] are as follows:

Permutational Isomerization = an individual rearrangement or reorganization with a characteristic pathway of motion and result.

Mechanism = Motionwise equivalent permutational isomerizations, cf. [73].

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$$\frac{d[(14)]}{dt} \Big/ \frac{d[(\overline{14})]}{dt} = k_{(12)\rightarrow(13)} \cdot k^{-1}_{(12)\rightarrow(16)} \cdot k_{(13)\rightarrow(14)} \cdot k^{-1}_{(16)\rightarrow(\overline{14})} \times (k_{(13)\rightarrow(12)} + k_{(13)\rightarrow(14)})^{-1} \times (k_{(16)\rightarrow(12)} + k_{(16)\rightarrow(\overline{14})})$$

which reduces to

$$k_{(12)\rightarrow(13)}\, k^{-1}_{(12)\rightarrow(16)} \text{ if } \quad k_{(13)\rightarrow(12)} \ll k_{(13)\rightarrow(14)} \text{ and } k_{(16)\rightarrow(12)} \ll k_{(16)\rightarrow(\overline{14})}.$$

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Syntheses of Heterocycles by Intramolecular Acylation of Nitrile-Hydrogen Halide Adducts

By Gerhard Simchen and Günther Entenmann[*]

Five-membered, six-membered, and seven-membered aza-, diaza-, and thiazaheterocycles can be prepared by cyclization of ω-cyano carboxylic acid halides in the presence of hydrogen halides in aprotic solvents. Nitrile-hydrogen halide adducts occur as intermediates in this novel heterocycle synthesis of wide application. The acylating cyclizations of nitriles in protonic media, which proceed *via* imidic esters or amides, are not discussed.

1. Introduction

Heterocycle syntheses with nitriles as reactants are very numerous. The nitrile group often acts only as an electrophile in these syntheses, *i.e.* only the carbon atom is incorporated into the ring system, with formation of amino-substituted heterocycles[1,2]. Ring closure reactions with incorporation of the entire nitrile group are usually preceded by the conversion of this group into an imidic ester or a carboxamide group[3–5]. Developments of the past 15 years include syntheses of heterocycles from nitriles by 1,3-dipolar cycloaddition[4] and on the basis of nitrilium salts[6–8]. These syntheses will not be discussed here.

The nitrile nitrogen is only weakly nucleophilic. Thus the presence of Lewis acids is necessary for the formation of alkylnitrilium and acylnitrilium salts[9]. Only very reactive acyl halides, such as malonyl chloride, react directly with nitriles to form heterocycles[10,11]. An intramolecular acylation leading to heterocycles is possible with hydrogen halide adducts of ω-cyanoacyl chlorides.

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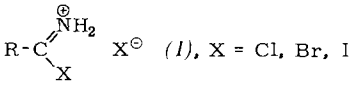
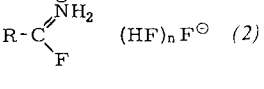
2. Nitrile-Hydrogen Halide Adducts

Reaction products of nitriles with hydrogen halides, though discovered by *Gautier*[12] in 1867, received little attention until recently. In 1964, *Allenstein et al.*[13,14] succeeded in establishing the structure of adducts of nitriles or thiocyanates with hydrogen chloride, bromide, and iodide. The isolable, thermally unstable substances (the adduct of acetonitrile and hydrogen chloride decomposes at 6 °C) were found to be compounds of the imidium acid halide halide (amide halide) type *(1)*. Their stability increases with the acidity of the hydrogen halide.



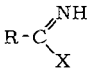
(1), X = Cl, Br, I

Adducts with complex anions are more stable, comparable with the "amide fluorides" *(2)*[15].



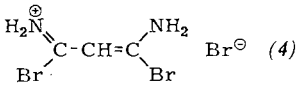
(2)

Imidoyl halides having the structure *(3)* have not so far been isolated[16,17]. The addition of one mole of HX evidently increases the basicity to such a degree that a further



(3)

mole of HX can be rapidly taken up. Imidoyl halides are postulated not only for the formation of the "amide halides" *(1)* but also for many reactions of nitriles that are catalyzed by hydrogen halides. The adduct *(4)* of malodinitrile and hydrogen bromide deserves mention[18]. In this case a 1:1 adduct is stabilized, as it were, by tautomerization to the α-bromoenamine.



(4)

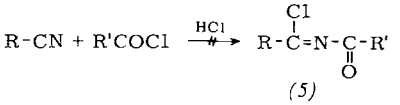
Nitrile-hydrogen halide adducts of the type *(1)* react with nucleophiles such as water, alcohols, and carboxylic acids[19]. The trimerization of nitriles to *s*-triazines may also belong to this class of reactions.

The course of the synthesis of many heterocycles from α,ω-dinitriles with hydrogen halides is uncertain. *Johnson* and *Madronero*[6] have invoked nucleophilic attack of a nitrile group on an "amide bromide" function in their interpretation.

3. Electrophilic Reactions on Nitrile-Hydrogen Halide Adducts

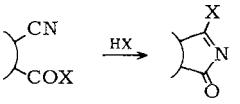
The increased nucleophilicity of the adducts in comparison with the nitriles should facilitate electrophilic reactions on the nitrogen. It should not, however, be overlooked that such addition compounds are present only in low concentrations, particularly at elevated temperatures. The isolation of *N*-acylation products therefore depends on the possibilities of stabilizing them.

Initial attempts to prepare *N*-acylimidoyl chlorides *(5)* by reaction of nitriles with acyl chlorides in the presence of hydrogen chloride[20] were unsuccessful.



(5)

When this reaction was applied to ω-cyanoacyl halides *(6)*, however, a novel synthesis of wide application was found for five-membered, six-membered, and seven-membered heterocycles. Significantly, the synthesis leads directly

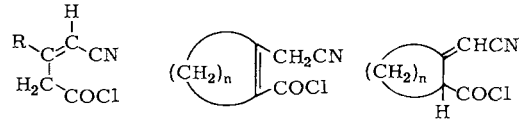


(6) *(7)*

to a heterocycle having a reactive halogen atom. The initially formed cyclic *N*-acylimidoyl halides *(7)* are stabilized in many cases by prototropy (see Section 4).

3.1. 6-Halo-2-pyridones

Non-cyclic esters of β-keto acids react with cyanoacetic acid to form esters of *cis*- and *trans*-β,γ-unsaturated γ-cyano carboxylic acids[21,22], from which the acids are obtained by hydrolysis, and the acyl chlorides *(8a)* are then obtained as crude products by reaction with phosphorus pentachloride. The corresponding cycloalkanecarboxylic acids give mixtures of the α,β- *(8b)* and β,γ-unsaturated acyl chloride *(8c)* in these reactions.



(8a), R = CH_3, C_6H_5 *(8b)*, n = 3, 4, 5 *(8c)*, n = 3, 4, 5

The acyl chlorides *(8a)* and *(8b)/(8c)* in the pure form remain unchanged in inert solvents. However, if hydrogen chloride is passed into solutions of these substances in ether/di-*n*-butyl ether, with subsequent heating to 50–80°C, one obtains 6-chloro-2-pyridones *(9a)* and *(9b)*[22,23] (Table 1)[*]. Since the ring closure does not occur in the absence of hydrogen chloride, the acylation must take place on an intermediate hydrogen chloride adduct.

Table 1. 6-Chloro-2-pyridones *(9a)* and *(9b)* from *(8a)* and from *(8b)/(8c)*.

	R/*n*	Conditions	Yield [%][a]	M.p.[°C]
(9a),	CH_3	6 h, 50°C	37	156–158
(9a),	C_6H_5	6 h, 50°C	63	166–168
(9b),	3	4 h, 60°C	35	182–184
(9b),	4	7 h, 80°C	38	187–190

[a] The yields are based on the carboxylic acids from which *(8a)* and *(8b)/(8c)* are derived.

Adducts with hydrogen bromide and with hydrogen iodide are more nucleophilic and thermally more stable than those with hydrogen chloride. This is confirmed by the extremely fast cyclization of *(8a)* and *(8b)/(8c)* (15–30 min at 0°C) in the presence of hydrogen bromide or hydrogen iodide[24]. The initial products are salt-like adducts of the hydrogen halides with 6-bromo-2-pyridones and 6-iodo-2-pyridones. The 6-halo-2-pyridones *(10a)* and *(10b)* are obtained from the adducts by treatment with aqueous sodium hydrogen carbonate solution (Table 2).

[*] It should be noted that the mixture *(8b)/(8c)* is converted exclusively into *(9b)*.

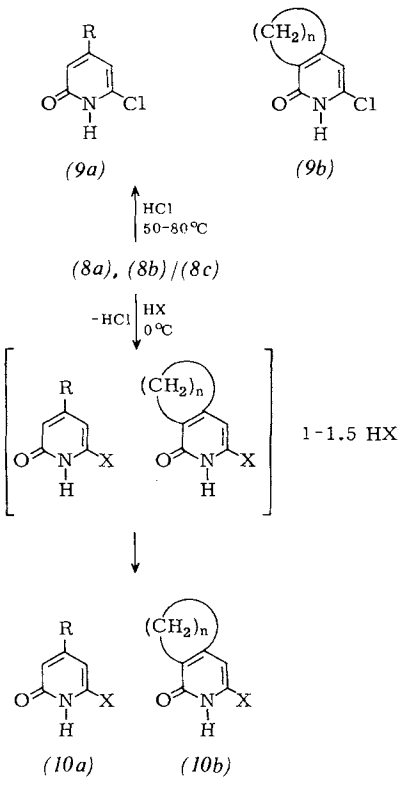


Table 2. 6-Halo-2-pyridones *(10a)* and *(10b)* from *(8a)* and from *(8b)/(8c)*.

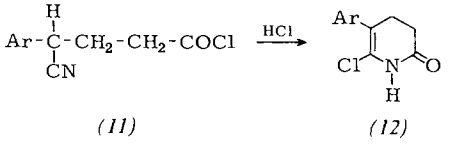
	R/*n*	X	Conditions	Yield [%][a]	M.p.[°C]
(10a),	CH_3	Br	30 min, 0°C	24	149–151
(10a),	C_6H_5	Br	30 min, 0°C	80	174–176
(10a),	C_6H_5	I	15 min, 0°C	67	199–201
(10b),	3	Br	30 min, 0°C	24	174–175
(10b),	4	Br	30 min, 0°C	38	195–196
(10b),	4	I	15 min, 0°C	40	192–193
(10b),	5	Br	30 min, 0°C	32	171

[a] The yields are based on the carboxylic acids from which *(8a)* and *(8b)/(8c)* are derived.

3.2. 6-Chloro-3,4-dihydro-2(1*H*)-pyridinones

The *N*-acylimidoyl halides formulated as precursors of the 2-pyridones *(9)* and *(10)* are stabilized by formation of the ring-conjugated pyridone system. The question whether this is essential for the ring closure can be examined in the reaction of 4-aryl-4-cyanobutyryl chlorides *(11)*[25] with hydrogen chloride. The compounds *(11)* can be distilled unchanged at temperatures above 100°C. However, if solutions of *(11)* in dioxane saturated with hydrogen chloride are heated for 6 h at 60°C, 6-chloro-5-aryl-3,4-dihydro-2(1*H*)-pyridinones *(12)* are formed in excellent yields[25] (Table 3).

The driving force of the cyclization is evidently the formation of the α-chloroenamide structure in *(12)*. If the



(11) *(12)*

Table 3. 6-Chloro-5-aryl-3,4-dihydro-2(1*H*)-pyridinones *(12)* from *(11)*.

Ar	Yield [%]	M.p.[°C]
Phenyl	80	180–184
4-Chlorophenyl	79	193–195
4-Methoxyphenyl	88	175–178
4-Nitrophenyl	85	240–245

γ-hydrogen in *(11)* is replaced by a methyl group, the ring closure does not occur[25].

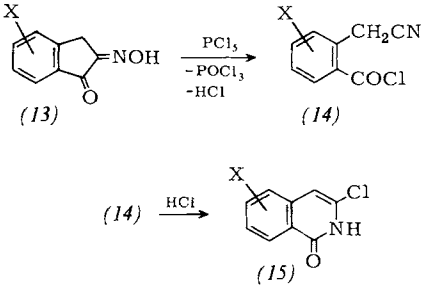
3.3. Halogenated Isoquinolines

In view of the great importance and the widespread use of isoquinolines, it would be of interest to synthesize them on the basis of the principle described. Most of the earlier isoquinoline syntheses involve intramolecular electrophilic substitution on the benzene ring. Satisfactory yields are therefore obtained only if the carbocyclic ring is activated by suitable +M or +I substituents[26–28]. An interesting method that was recently described for the preparation of 1,3-dichloroisoquinolines from arylacetonitriles and phosgene in the presence of hydrogen chloride offers no improvement[29]. Isoquinoline derivatives with activating substituents on C-8 were practically unknown in the past, since the cyclization occurs almost exclusively in position 4 with respect to the activating group[28]. Little investigation has been devoted to syntheses that give isoquinolines in good yields irrespective of the nature and position of the substituent; examples are the amidation of isocoumarins[30], the reaction of homophthalic acids with amines[27], and the cyclization of *o*-cyanomethylbenzonitriles[31] with hydrogen bromide, which leads to 1-bromo-3-aminoisoquinolines.

3.3.1. 3-Halo-1-isoquinolones

The starting materials for the cyclization are 2-cyanomethylbenzoyl chlorides *(14)*, which are obtained either from phthalides by reaction with potassium cyanide[32] and then with phosphorus pentachloride or by Beckmann rearrangement of the second kind[33] from 2-oximino-1-indanones *(13)*[34]. 2-Oximino-1-indanones are readily obtainable by nitrosation of 1-indanones with alkyl nitrites in the presence of hydrochloric acid[34].

Saturation of solutions of 2-cyanomethylbenzoyl chlorides *(14)* in dioxane with hydrogen chloride and heating for a few hours at 60—70°C leads to 3-chloro-1-isoquinolones *(15)*[34,35] (Table 4).



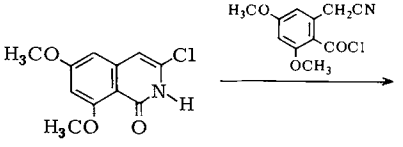
(13) *(14)* *(15)*

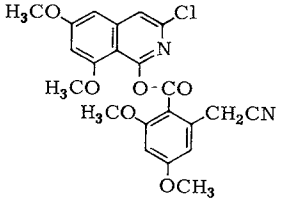
Table 4. 3-Chloro-1-isoquinolones *(15)* from 2-cyanomethylbenzoyl chlorides *(14)*.

X	Yield [%] [a]	M.p. [°C]
H	76	210–215
5-Methyl	75	243.5
7-Methyl	72	223–224
5-Methoxy	72	246–247
6-Methoxy	100	228–229
7-Methoxy	50	241
7-Chloro	68	253–254
6,7-Dimethoxy	74	264–265
6,8-Dimethoxy	77	201–202
6,7,8-Trimethoxy	40	211–212
8-Chloro-5-methyl	96	250–251
5-Chloro-8-methyl	70	281–282
5,8-Dimethyl	89	244–245
7-Nitro	100	323–325

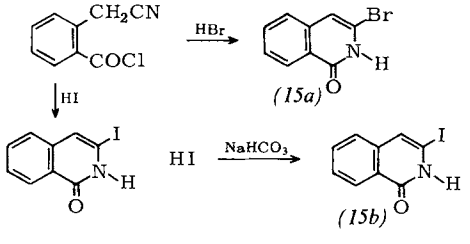
[a] The yields of *(15)* are based on 2-oximino-1-indanones *(13)*.

The rate of the cyclization increases with the hydrogen chloride concentration. If the reaction is carried out at low hydrogen chloride concentrations, *e.g.* in di-*n*-butyl ether, side reactions due to acylation of already formed *(15)* are observed in the case of inert acyl chlorides *(14)*[34].





3-Bromo-1-isoquinolone *(15a)* and 3-iodo-1-isoquinolone *(15b)* are obtained particularly readily and in quantitative yield from 2-cyanomethylbenzoyl chloride with hydrogen bromide and hydrogen iodide respectively in ether at 0 °C[34] (2 h and 20 min respectively).



3.3.2. 1,3-Dichloroisoquinolines

By analogy with the synthesis of 3-chloro-1-isoquinolones *(15)*, it seemed reasonable to attempt the preparation of 1,3-dichloroisoquinolines *(16)* by a "single-reactor method" from 2-oximino-1-indanones *(13)*. By Beckmann rearrangement of *(13)* with phosphorus pentachloride in phosphorus oxide chloride as the solvent, saturation with hydrogen chloride, and heating for a few hours at 60 °C, one obtains 3-chloro-1-isoquinolones *(15)* as intermediates. After further addition of an equimolar quantity of phosphorus pentachloride and heating at 80–100 °C, the components react to form 1,3-dichloroisoquinolines *(16)*[36]. 2-Cyanomethylbenzoic acid is used as the starting material for the preparation of 1,3-dichloroisoquinoline *(16a)* (Table 5).

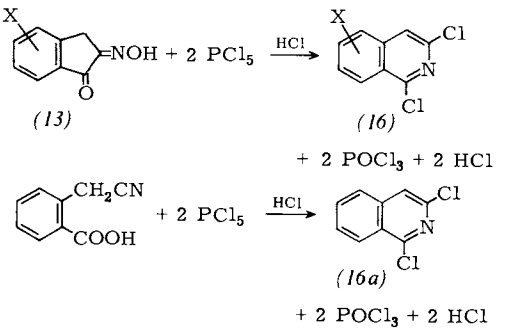


Table 5. 1,3-Dichloroisoquinolines *(16)* from 2-oximino-1-indanones *(13)*.

X	Yield [%]	M.p. [°C]
H [a]	61	120
5-Methyl	85	121
7-Methyl	80	113–114
5-Methoxy	80	166–167
6-Methoxy	57	91– 93
7-Methoxy	62	169–170
7-Chloro	77	166–168
6,7-Dimethoxy	76	200–201
8-Chloro-5-methyl	90	146–148
5-Chloro-8-methyl	70	165–166
5,8-Dimethyl	44	136–137
7-Nitro	64	176–180

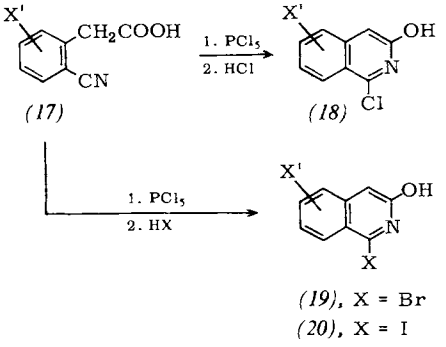
[a] *(16a)*; prepared from 2-cyanomethylbenzoic acid.

3.3.3. 1-Halo-3-hydroxyisoquinolines

A feature common to all the syntheses described so far is the electrophilic attack of chlorocarbonyl groups on hydrogen halide adducts of aliphatic nitriles, *i.e.* of compounds whose cyano groups are not directly attached to an aromatic nucleus. Whether the much less stable hydrogen halide adducts of aromatic nitriles can be acylated should be shown by corresponding reactions with (2-cyanophenyl)-acetyl chlorides. (2-Cyanophenyl)acetic acids *(17)* are obtained from oxindoles by alkaline hydrolysis followed by a Sandmeyer reaction with copper(I) cyanide, or from (2-nitrophenyl)acetic acids, which are reduced and again subjected to a Sandmeyer reaction[37–39].

If (2-cyanophenyl)acetic acids *(17)* are first converted into the acyl chlorides by reaction with phosphorus pentachloride in di-*n*-butyl ether or ether/di-*n*-butyl ether at 20 °C, followed by saturation of these solutions with hydrogen chloride and standing for about 12 h, 1-chloro-3-hydroxyisoquinolines *(18)* precipitate in excellent yields[39,40]. In the preparation of 1-bromo- *(19)* and 1-iodo-3-hydroxyisoquinolines *(20)*[39], after the reaction of *(17)* with phosphorus pentachloride, the phosphorus oxide chloride and the solvent are first distilled off and the crude product is taken up in ether. Hydrogen bromide

or hydrogen iodide is introduced at 0 °C until the solution is saturated; after a few minutes, *(19)* or *(20)* is obtained in the form of the hydrogen halide adduct (Table 6).



(19), X = Br
(20), X = I

Table 6. 1-Halo-3-hydroxyisoquinolines *(18)*–*(20)* from (2-cyanophenyl)acetic acids *(17)*.

X'	X	Yield [%]	M.p. [°C]
(18), H	Cl	79	205–206
(19), H	Br	83	179–182
(20), H	I	81	154–157
(18), 6-Methyl	Cl	84	194–196
(19), 6-Methyl	Br	82	188–190
(20), 6-Methyl	I	70	165–167
(18), 7-Methyl	Cl	94	194–196
(19), 7-Methyl	Br	84	193–195
(18), 6-Chloro	Cl	80	219–221
(19), 6-Chloro	Br	70	204–206
(18), 6-Bromo	Cl	70	226–227
(19), 6-Bromo	Br	89	197–199
(20), 6-Bromo	I	85	180–182
(18), 6-Methoxy	Cl	72	211
(19), 6-Methoxy	Br	73	191–193
(20), 6-Methoxy	I	85	180–182
(18), 7-Methoxy	Cl	70	230–232
(18), 6,7-Dimethoxy	Cl	69	226–227
(19), 6,7-Dimethoxy	Br	75	207–210
(20), 6,7-Dimethoxy	I	61	220–222

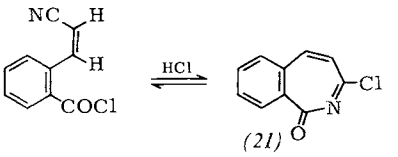
Investigations on the reaction course showed that though *(18)* is formed more slowly than the chlorine analog *(16)*, the differences are small and are not noticeable at high hydrogen halide concentrations[41].

The syntheses described in Sections 3.3.1 to 3.3.3 all give isoquinolines in equally good yields, irrespective of the nature and position of the substituents in the aromatic compounds. The isoquinoline derivatives in Tables 4–6 have not been described before or were hitherto obtainable only with considerable difficulty.

3.4. 3-Chloro-2-benzazepin-1-one

In all the ring closure reactions discussed so far the final product is stabilized by a proton shift (cf. Section 3.2).

The question whether the proton shift is a necessary criterion, *i.e.* whether cyclization does not also occur if bond systems obeying the Hückel rule are formally to be expected directly, has been investigated for the reaction of 2-(*cis*-2-cyanovinyl)benzoyl chloride with hydrogen chloride in dioxane (70 °C, 5 h). The reaction did in fact lead to the previously unknown 3-chloro-2-benzazepin-1-one (benzazatropone) *(21)*, which may be regarded as a heteroaromatic system[42,43].



(21)

Yields above 50% were unobtainable; the reaction is an equilibrium process.

3.5. Diazaheterocycles

As can be seen from the heterocycle syntheses described in the foregoing sections, nitrile-hydrogen halide adducts can be acylated on the nitrogen if stabilization of the cyclic *N*-acylimidoyl halide is possible by tautomerization (Sections 3.1 and 3.2) or by formation of a ring-conjugated 6π-electron system (Sections 3.3 and 3.4).

Substantial expansions of the synthesis result from variation of the acyl halide function. For example, stable heterocycles should also be obtained on replacement of the chlorocarbonyl group by a chlorocarbonylamino group.

3.5.1. 4-Halo-2-quinazolones

Reaction of *o*-cyanophenyl isocyanates *(22)* with hydrogen halide at room temperature in di-*n*-butyl ether leads first to carbamoyl halides *(23)*, which cyclize at about 70 °C in the presence of an excess of hydrogen halide to form 4-halo-2-quinazolones *(24)*[44] (Table 7).

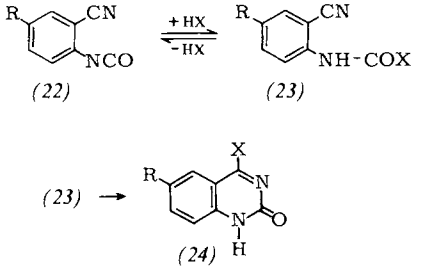


Table 7. 4-Halo-2-quinazolones *(24)* from *(22)*.

X	R	Yield [%]	M.p. [°C]
Chloro	H	87	213
Bromo	H	78	[a]
Chloro	Bromo	77–85	250–255

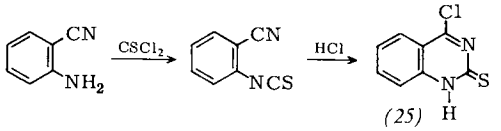
[a] The compound is susceptible to hydrolysis. The melting points found in several experiments range from 280 to 320 °C.

The synthesis of 4-chloro-2-quinazolones can also be carried out as a "one-reactor process" by introduction of phosgene into a suspension of 2-cyanoanilinium chloride in dibutyl ether at 120 °C, followed by the introduction of hydrogen chloride at 80 °C.

Reference should be made at this point to the formally similar reaction of nitriles with phosgene to form 6-chloro-2,5-disubstituted 4-pyrimidones as described by *Yanagida et al.*[45]; however, the ring closure in this case is carried out by intramolecular *C*-acylation of an enamine.

3.5.2. 4-Chloro-2-thioquinazolone

o-Cyanophenyl isothiocyanate, which is readily obtainable from *o*-cyanoaniline and thiophosgene, can be cyclized with hydrogen chloride in analogy with the reactions described above to give 4-chloro-2-thioquinazolone *(25)*. The yield is 70%[44].



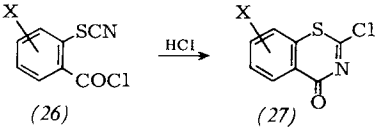
(25)

3.6. 1,3-Thiazaheterocycles

Cyclization of α,β-unsaturated β-thiocyanatoacyl chlorides with hydrogen halides should yield heterocycles that are formally derived from 3-chloro-2-benzazepin-1-one *(21)* by replacement of a vinylene grouping by sulfur.

3.6.1. 2-Chloro-1,3-benzothiazin-4-ones

When a solution of an *o*-thiocyanatobenzoyl chloride *(26)* in an ether/dibutyl ether mixture saturated with hydrogen chloride is heated (5 h, 70°C), 2-chloro-1,3-benzothiazin-4-ones *(27)* are obtained in good yields[46] (Table 8). Similarly, 2-chloronaphtho[2,3-*e*]-[1,3]-thiazin-4-one *(27a)* is obtained from 3-thiocyanato-2-naphthoyl chloride.



(26) *(27)*

Table 8. 2-Chlor-1,3-benzothiazin-4-ones *(27)* from *(26)*.

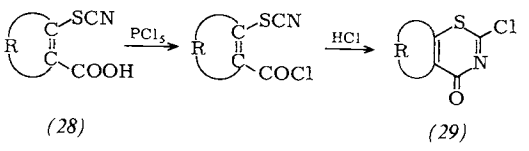
X	Yield [%]	M.p.[°C]
H	74	115–117
7-Chloro	73	149–150
6-Chloro	74	178
7-Methoxy	88	164–165
6-Methoxy	61	162
7-Nitro	73	188–190
6-Nitro	80	140–142
(27a)	76	176–178

The acyl chlorides *(26)* need not be isolated; the crude products obtained by reaction of the *o*-thiocyanatobenzoic acids with phosphorus pentachloride can be cyclized to form *(27)*.

After these investigations had been closed, we learned of a method for the preparation of 2-chloro-1,3-benzothiazin-4-ones by reaction of 2-thiocyanatobenzoic acids with thionyl chloride in the presence of catalytic quantities of dimethylformamide[47].

3.6.2. 2-Chloro-1,3-thiazin-4-ones

On reaction of *cis*-β-thiocyanatoacrylic acid *(28a)* in ether at 0°C with phosphorus pentachloride and introduction of dry hydrogen chloride into the solution, 2-chloro-1,3-thiazin-4-one *(29a)* precipitates[48]. The derivatives *(29b)* and *(29c)* are obtained in a similar manner (Table 9).



(28) *(29)*

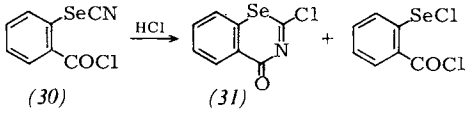
Table 9. 2-Chloro-1,3-thiazin-4-ones of the type *(29)*.

	R	Yield [%]	M.p.[°C]
(29a)	—H H—	52	95–97
(29b)	—$(CH_2)_3$—	53	77–79
(29c)	—$(CH_2)_4$—	45	78–80

cis-β-Thiocyanatoacrylic acid *(28a)* is formed by addition of potassium thiocyanate to acetylenemonocarboxylic acid in dilute sulfuric acid. The acids *(28b)* and *(28c)* are prepared by reaction of 2-chloro-1-formyl-1-cyclopentene and 2-chloro-1-formyl-1-cyclohexene, respectively, with potassium thiocyanate, followed by oxidation with chromium trioxide.

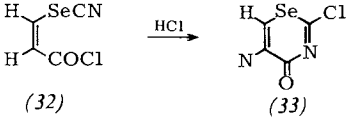
3.6.3. 2-Chloro-1,3-selenazin-4-ones

When 2-selenocyanatobenzoyl chloride *(30)* is heated for 5 hours in dioxane saturated with hydrogen chloride, one obtains 2-chloro-1,3-benzoselenazin-4-one *(31)* having a melting point of 125—126 °C in 59% yield[40,46]. 2-Chloroselenenylbenzoyl chloride is also formed by cleavage of *(30)*[46].



(30) *(31)*

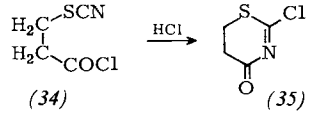
The cyclization of β-selenocyanatoacryloyl chloride *(32)* to form 2-chloro-1,3-selenazin-4-one *(33)* proceeds in poor yield with hydrogen chloride in dibutyl ether at 80°C. The main reaction here is probably the cleavage of the selenocyanate group to give selenenyl chloride and hydrogen cyanide[48].



(32) *(33)*

3.6.4. 2-Chloro-5,6-dihydro-1,3-thiazin-4-one

If hydrogen chloride is led into a solution of β-thiocyanatopropionyl chloride *(34)* in ether at 0°C, 2-chloro-5,6-dihydro-1,3-thiazin-4-one *(35)* crystallizes out after one hour[48]. It was thus possible, by acylation of a nitrile-hydrogen halide adduct, to synthesize a heterocyclic



(34) *(35)*

compound that is not stabilized by tautomerization or by formation of a 6π-electron system. *(35)* is not very stable,

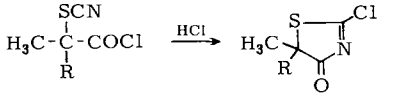
and is reconverted into *(34)* on standing for several days at room temperature. *(35)* also exhibits a number of peculiarities in its reactions. Whereas the halogen in the thiazinones *(27)* and *(29)* is smoothly replaced in reactions with nucleophiles, ring cleavage predominates in *(35)*.

Perhydro-1,3-thiazine-2,4-dione is obtained by hydrolysis of *(35)*[48] or by reaction of β-thiocyanatopropionic acid with thionyl chloride[49].

3.6.5. 2-Chloro-4-thiazolones

Though many six-membered and seven-membered heterocycles have been synthesized, it is not yet known whether smaller rings are also obtainable by cyclizing acylation of nitrile-hydrogen halide adducts. As an example we chose the cyclization of α-thiocyanatoacyl chlorides, partly because of the interesting properties of the expected 4-thiazolones.

On saturation of a solution of α-thiocyanatopropionyl chloride or of α-thiocyanatoisobutyryl chloride in absolute ether with dry hydrogen chloride at −20 to 0°C, the 5-substituted 2-chloro-4-thiazolone *(36a)* or *(36b)* crystallizes out after a short time[50] [*(36a)*, m.p. 55°C, yield 64%; *(36b)*, m. p. 81–83°C, yield 74%].

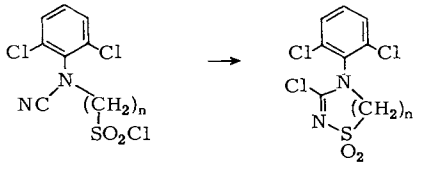


(36a), R = H
(36b), R = CH_3

5,5-Dimethyl-2-chloro-4-thiazolone *(36b)* is a stable crystalline substance; *(36a)* decomposes on prolonged standing at room temperature, with development of a yellow color.

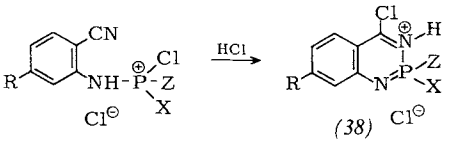
3.6.6. Ring Systems with Three Hetero Atoms

The extreme versatility of the cyclization reaction described here is underlined by syntheses of other heterocyclic systems. *Toldy* and *Sohár*[51] described the preparation of 3-chloro-5,6-dihydro-1,2,4-thiadiazine 1,1-dioxides *(37a)* and 3-chloro-5*H*-6,7-dihydro-1,2,4-thiadiazepine 1,1-dioxides *(37b)* by heating ω-(*N*-aryl-*N*-cyanamino)alkanesulfonyl chlorides. This reaction probably also proceeds *via* intermediate nitrile-hydrogen halide adducts.



(37a), n = 2
(37b), n = 3

4-Chloro-3*H*-1,3,2-benzodiazaphosphorinium chlorides *(38)* are obtained according to *Schmidpeter* and *Schindler*[52] by cyclization of 2-cyanoanilinophosphonium chlorides with hydrogen chloride.

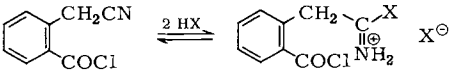


(38)

R = H, CH_3
X = C_6H_5, CH_3, Cl
Z = C_6H_5, Cl

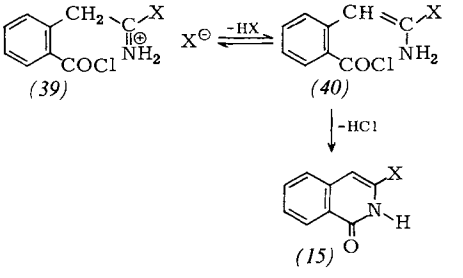
4. Course of the Reaction

Detailed investigations on the mode of formation of 3-halo-1-isoquinolones *(15)* have proved that nitrile-hydrogen halide 1,2-adducts *(39)* occur as intermediates.



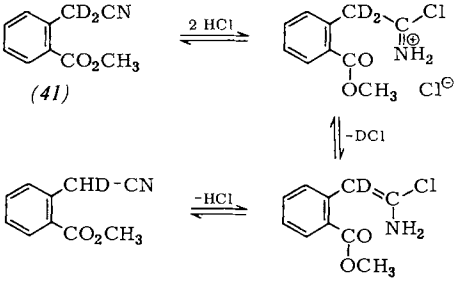
(39)

Since an electrophilic attack of the carbonyl group on the imonium group is not very probable, we assume that α-haloenamines *(40)* occur as intermediates.



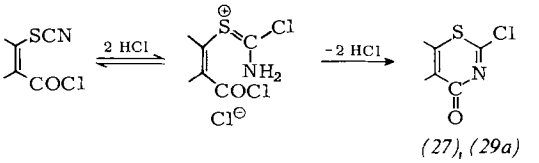
(39) *(40)* *(15)*

The existence of α-haloenamines has been detected *e.g.* by D/H exchange on methyl [α,α-D_2]-2-cyanomethylbenzoate *(41)* with dry hydrogen chloride in dioxane at 50°C.



(41)

Intermediates having an analogous structure should also be possible in the cyclization of α,β-unsaturated β-thiocyanatoacyl chlorides to form *(27)* and *(29a)*.



(27), *(29a)*

However, nitrile-hydrogen halide 1,1-adducts cannot be ruled out as the true reactive intermediates at least in the ring closure reactions leading to *(18)*, *(21)*, *(24)*, and *(25)*.

We thank Prof. Dr. H. Bredereck for his generous support of our work. Thanks are also due to the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for material aid.

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Chemistry and Biology of the Acylneuraminic Acids

By Roland Schauer[*]

Acylneuraminic acids occupy an outstanding position both sterically and with respect to biological functions in gangliosides and in many glycoprotein molecules. Acylneuraminic acids are *N*-acylated and partly *O*-acylated derivatives of neuraminic acid, a polyhydroxyamino keto acid that has the properties of a carbohydrate and is therefore capable of forming a glycoside linkage. The present report provides a survey of our knowledge of the chemistry and biology of the acylneuraminic acids, which occur widely in particular in the animal kingdom.

1. Discovery and Elucidation of the Structure of the Acylneuraminic Acids

The first indication of the existence of the substances under discussion was obtained in 1927 by *Walz*[1] and by *Levene* and *Landsteiner*[2] when they heated glycolipids with orcinol in hydrochloric acid containing ferric chloride and observed a red-violet color (see Section 2). In 1936, *Blix*[3] isolated a monocarboxylic acid in the crystalline form from the "submaxillary mucin", the glycoprotein of the submandibular gland (glandula submaxillaris) of the ox; this acid, whose possible composition was given as $C_{14}H_{23}NO_{11}$, also gave a red-violet color with the orcinol-hydrochloric acid reagent. In 1941, by methanolysis of gangliosides of the brain, *Klenk*[4] obtained a substance having an acidic reaction, which he named "neuraminic acid" because of its origin in the nerve tissue. It was identified a year later as "methoxyneuraminic acid" (neuraminic acid β-methyl glycoside), the derivative of a polyhydroxyamino acid, having the composition $C_{10}H_{19}NO_8$[5].

N-Acetylneuraminic acid was first isolated in the crystalline form by *Klenk* and *Faillard*[6] and by *Klenk*, *Faillard*, and *Lempfrid*[7] from bovine submaxillary mucin by acid hydrolysis and from urinary mucin by the action of influenza viruses (see Section 7). Pure *N*-glycoloylneuraminic acid was obtained by *Blix*'s research group[8] in 1956 and by *Klenk* and *Uhlenbruck*[9] in 1957 from pig submaxillary mucin. Diacetylneuraminic and triacetylneuraminic acids were obtained by *Blix*[8, 10] from bovine and horse submaxillary mucins (see Section 4; other acylneuraminic acids are also described there).

The determination of the constitution of neuraminic acid took a long time, since it occurs in nature only in the form of acyl derivatives, which are also called sialic acids after a proposal by *Blix*, *Gottschalk*, and *Klenk*[11]. Only the functional groups of neuraminic acid, *i.e.* a carboxyl group, a reducing (glycoside) group, an amino group, and five hydroxyl groups, quickly became known[8, 12]. Further light was thrown on the chemistry of neuraminic acid by the first syntheses of *N*-acetylneuraminic acid *(1)*, which was achieved by *Cornforth et al.*[14, 15] from *N*-acetylglucosamine and oxalacetic acid ("activated pyruvic acid") on the basis of *Gottschalk*'s assumption[13] that *N*-acetylneuraminic acid is an aldol condensate of *N*-acetylglucosamine and pyruvic acid. This gave a substance that was completely identical with the substance isolated from the natural products. These experiments pointed to *N*-acetylglucosamine as a structural component of *N*-acetylneuraminic acid. However, *Comb* and *Roseman*[16] obtained *N*-acetylmannosamine *(2)* and pyruvic acid *(3)* by the action of an aldolase (see Section 7) on *N*-acetylneuraminic acid *(1)*, showing that the configuration of the substituents on C atoms 5 to 8 of neuraminic acid correspond to those of *N*-acetylmannosamine (Fig. 1). The successful syntheses of *N*-acetylneuraminic acid from *N*-acetylglucosamine[14, 15] are explained by the ease of epimerization of *N*-acetylglucosamine to *N*-acetylmannosamine in alkaline media[17, 18].

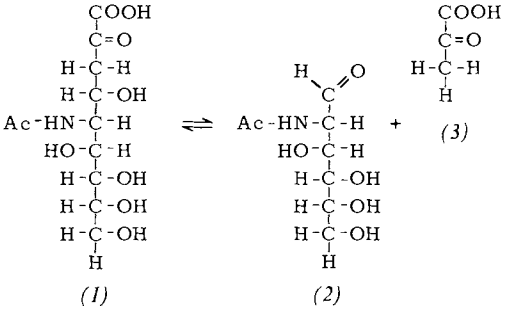

Fig. 1. Reversible cleavage of *N*-acetylneuraminic acid *(1)* into *N*-acetylmannosamine *(2)* and pyruvic acid *(3)* by the aldolase "acylneuraminate-pyruvate lyase" (see Section 7). Representation of the sugars (keto forms) in Fischer projection formulas.

After the determination of the configuration of the OH group on C-4 (on the right-hand side in the Fischer projection formula; see Fig. 1) by *Kuhn et al.*[19, 20], the stereochemistry of neuraminic acid was largely known, and it was possible to assign the following systematic name to *N*-acetylneuraminic acid: 5-acetamido-3,5-dideoxy-D-glycero-D-galactononulosaminic acid. Like all acylneuraminic acids, it occurs in the pyranose form (see Figs. 2, 6, 7)[21]. The absolute conformation of *N*-acetylneuraminic acid has recently been determined by NMR studies on the methyl ester of *N*-acetylneuraminic acid[22] and X-ray analysis of crystals of neuraminic acid β-methyl glycoside[23]. It corresponds to the 1C conformation according to the Reeves nomenclature (Fig. 2). According to these investigations, the anomeric hydroxyl group of the non-

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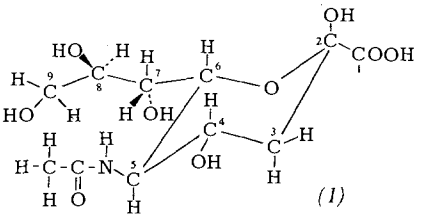
glycosidically bound neuraminic acid is arranged axially on C-2 (Fig. 2).

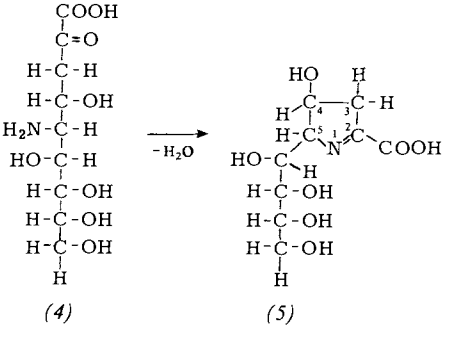


(1)

Fig. 2. *N*-Acetylneuraminic acid *(1)* in the pyranose form; 1C conformation. Reeves notation.

2. Properties of and Methods for the Detection of Acylneuraminic Acids

Unsubstituted neuraminic acid *(4)* is incapable of existence, since it cyclizes immediately by condensation of the amino group on C-5 with the carbonyl group on C-2 to form an internal Schiff base, 4-hydroxy-5-(1,2,3,4-tetrahydroxybutyl)-Δ^1-pyrroline-2-carboxylic acid *(5)*[24] (Fig. 3). This ring closure is prevented by the glycoside linkage *e.g.* of a methyl group to C-2 ("neuraminic acid β-methyl glycoside")[4] or by acylation of the amino group, as is the case in the naturally occurring or synthetically prepared neuraminic acid derivatives (see Sections 4 and 5).



(4) *(5)*

Fig. 3. Spontaneous cyclization of neuraminic acid *(4)*, which cannot exist, to form 4-hydroxy-5-(1,2,3,4-tetrahydroxybutyl)-Δ^1-pyrroline-2-carboxylic acid *(5)*.

The acylneuraminic acids are colorless substances that can be crystallized from mixtures of acetic acid, ethanol, or dioxane with water, are stable in the dry state, and melt with decomposition below 200 °C[21, 25]. They dissolve readily in water, and in aqueous solution they rotate the plane of polarized light to the left[21, 25]; they are sparingly soluble in methanol (with the exception of the oligoacetylneuraminic acids; Section 4) and insoluble in ether. As α-keto acids, they are relatively strong acids and, depending on the nature of the *N* or *O* substituents, their p*K* values lie between 1.8 and 2.6[26, 27].

Whereas free acylneuraminic acids decompose readily both in alkaline and in acidic solution, glycosidically bound acylneuraminic acids are moderately stable toward alkalis. In alkaline media, free acylneuraminic acids realdolize to form pyruvate and *N*-acylmannosamines or *N*-acylglucosamines[28, 29] (cf. Fig. 1), or else pyrrole derivatives are formed[30]. In a reaction typical of α-keto acids, acylneuraminic acids are decarboxylated in 12% HCl at 100 °C; with concentrated H_2SO_4 they give carbon monoxide[8]. The decomposition proceeds slowly in dilute acids[31], with gradual formation of cherry red to dark brown products[32]. The degradation begins either with deacylation of the amino group followed by intramolecular ring closure of the resulting free neuraminic acid, or else enolization, dehydration, and elimination reactions lead to cyclization and polymerization of the molecules to form brown "humin substances"[33].

The products resulting from the acid degradation of the acylneuraminic acids form the basis of the Ehrlich and of the Svennerholm/Bial methods for the quantitative determination of acylneuraminic acids. In the "direct" Ehrlich reaction, a purple-red dye is formed when acylneuraminic acids are heated in hydrochloric acid solution with *p*-dimethylaminobenzaldehyde[21, 32]: the chromogen of this reaction is presumably the 5-tetrahydroxybutyl-2-pyrrolecarboxylic acid formed from neuraminic acid[21], which is trapped by the aldehyde. In the Svennerholm/Bial method, a violet dye is formed by heating acylneuraminic acid in hydrochloric acid with resorcinol[34] or with orcinol[35] and Fe^{3+} ions. This color is probably due to a methine dye[36], which is specific for neuraminic acid and is formed from it in a complicated sequence of reactions that has not yet been fully clarified.

Both of these methods are suitable for the determination of either glycosidically bound or free acylneuraminic acids. The periodic acid/thiobarbituric acid method of *Warren*[37] and *Aminoff*[38], on the other hand, responds only to free acylneuraminic acids. In this very sensitive method of analysis (detection limit 2—5 μg of *N*-acetylneuraminic acid), which is the most commonly used, the periodate oxidation of acylneuraminic acids yields β-formylpyruvic acid (HOOC—CO—CH_2—CHO[39]), which couples with 2-thiobarbituric acid to give a red dye.

3. Isolation of the Acylneuraminic Acids

Acylneuraminic acids mainly do not occur free in nature, but are attached to macromolecules by acid-labile α-glycoside linkages (see Section 4). The glycoside linkage can be broken either under particularly mild conditions with the commercially obtainable enzyme neuraminidase (see Section 7[40, 32, 41]) or with dilute acids[21], *e.g.* with 0.05—0.1 N H_2SO_4 or HCl (80 °C, 1 h[21, 32, 42, 43]). (For the cleavage of acylneuraminic acids having very readily hydrolyzable *O*-acetyl groups, the hydrolysis conditions must be even milder: 0.01 N HCl, 70 °C, 1 h[40].) The acylneuraminic acid released is dialyzed out against water, purified by ion exchange chromatography, and fractionated on cellulose powder in butanol/propanol/water (Ref. [40], cf. Fig. 4).

The acylneuraminic acids are identified by thin layer (radio)chromatography on silica gel and cellulose in several systems[40, 44]. The number of ester groups is determined with hydroxylamine by the method of *Hestrin*[45], and their position on the neuraminic acid skeleton is found polarographically with periodic acid[40]. Good progress is being

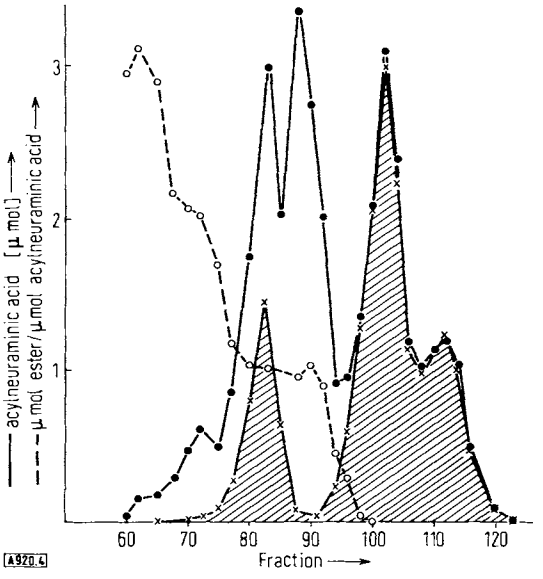


Fig. 4. Acylneuraminic acids liberated from bovine submaxillary mucin by acid hydrolysis. Fractionation of the acylneuraminic acid mixture by chromatography on cellulose in butanol/propanol/water (1 : 2 : 1) [40]. Determination of the acylneuraminic acid contents of individual fractions with orcinol/Fe^{3+} (• — •) or with periodic acid/thiobarbituric acid (× — ×). μmoles of ester groups per μmole of acylneuraminic acids (o- - -o). Fractions 60—75: *N*-acetyl-tri-*O*-acetyl- and *N*-acetyl-di-*O*-acetylneuraminic acids; 76—85: *N*-acetyl-8-*O*-acetylneuraminic acid *(10)*; 86—95: *N*-acetyl-7-*O*-acetylneuraminic acid *(9)*; 96—108: *N*-acetylneuraminic acid *(1)*; 109—123: *N*-glycoloylneuraminic acid *(7)*. (For further explanation see Section 4.)

made in the development of gas-chromatographic methods for the quantitative and qualitative analysis of the acylneuraminic acids[46].

The isolation of neuraminic acid as neuraminic acid β-methyl glycoside, which is used as a starting material for the synthesis of acylneuraminic acids (Section 5), is easily achieved in a yield of about 80% on the basis of well-known methods[47] by methanolysis (1 N H_2SO_4 in anhydrous methanol) of acylneuraminic acids, which occur abundantly in glycoproteins from bovine submandibular glands or from the nests of oriental swallows[25,48].

4. Naturally Occurring Acylneuraminic Acids

Acylneuraminic acids have so far been found only in animal material and in some bacteria, but never in plants[49]. They are of widespread occurrence as components of glycoproteins and glycolipids both in invertebrates and in vertebrates in cells and in body fluids[21,32] (Section 8). However, free non glycosidically bound acylneuraminic acids can be detected in the tissue only in small quantities[50,51]. The observation by *Montreuil et al.*[52] of the excretion of up to 7.2 g of free *N*-acetylneuraminic acid daily by a patient aged three years ("sialuria") is so far an isolated case.

The acylneuraminic acids generally occupy the non-reducing end of the heterooligosaccharide chains in glycoproteins[32] and in gangliosides[53], where they are bound by a glycoside linkage to hydroxyl groups of the galactose, the *N*-acetylgalactosamine, or a second *N*-acetylneuraminic acid molecule. Examples of linkages that occur are *N*-acetylneuraminic acid(2→3)-galactose[*][54–56] in 3'-sialyllactose and in gangliosides, *N*-acetylneuraminic acid(2→6)-*N*-acetylgalactosamine[57] in the submaxillary mucin of sheep, and *N*-acetylneuraminic acid(2→8)-*N*-acetylneuraminic acid in gangliosides[58] and in colominic acid (see below)[59]. In all the natural neuraminic acid glycosides investigated so far, the ketoside linkage of the acylneuraminic acids (assuming that *N*-acetylneuraminic acid belongs to the D series[54,60,61]) has the α configuration. As was mentioned in Section 3, this bond is acid-labile and is readily attacked by enzymes[61] (Fig. 5).

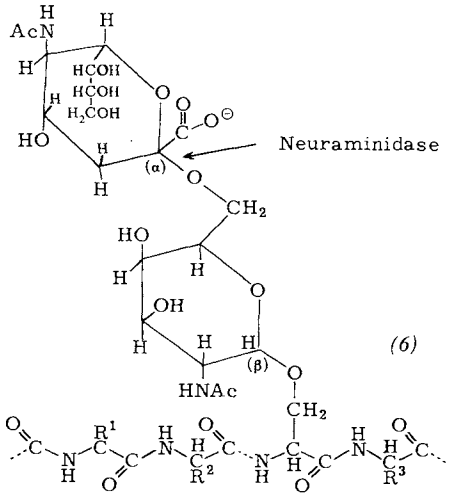
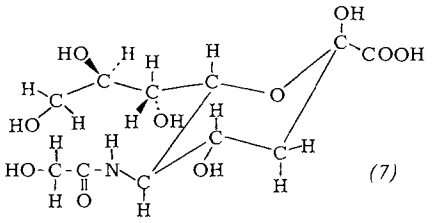


Fig. 5. Part of a glycoprotein molecule *(6)* of sheep submaxillary mucin to demonstrate the α-glycoside linkage of the *N*-acetylneuraminic acid to other carbohydrate residues, in this case to C-6 of *N*-acetylgalactosamine. The disaccharide group is attached by an *O*-glycoside linkage to hydroxyl groups of serine or threonine residues of the protein chain (from [32, 57]).

The most widely occurring natural derivative of neuraminic acid is *N*-acetylneuraminic acid *(1)*. This occurs as a polymer, known as colominic acid, in the culture filtrate of *Escherichia coli* K-235[59]. The acylneuraminic acid fraction from the submaxillary mucin of sheep[8] and from glycoproteins of human organs and erythrocytes[6,7,62] also contains mainly *N*-acetylneuraminic acid. However, a mixture of acylneuraminic acids occurs in many animal materials. Apart from *N*-acetylneuraminic acid *(1)*, which is surprisingly always present, these are mainly *N*-glycoloylneuraminic acid *(7)* (Fig. 6) and a number of more highly acetylated neuraminic acids such as *(8)—(11)* (Fig. 7). In addition to the *N*-acetyl group the latter contain one or more acetic acid residues attached by ester linkages.

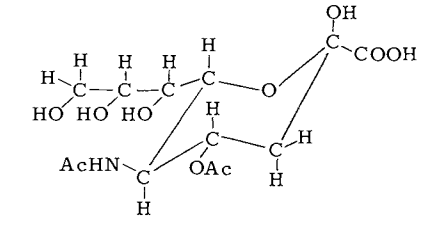
N-Glycoloylneuraminic acid *(7)* is of relatively widespread occurrence. The organ having a particularly high content of *N*-glycoloylneuraminic acid is the submandibular gland of the pig, in which *N*-glycoloylneuraminic acid accounts for about 90% of the total acylneuraminic acids[43,50]. *N*-Glycoloylneuraminic acid also occurs in various quantities *e.g.* in bovine erythrocytes[21], in serum glycoproteins[63], in bovine and horse submaxillary mucin[40], in the skin of calf fetuses[64], in gangliosides from horse erythrocytes[65], and in gangliosides from the brain of the hen[66].

[*] This notation means *e.g.* linkage of the glycoside hydroxyl group on C-2 of the *N*-acetylneuraminic acid to the hydroxyl group on C-3 of the galactose.

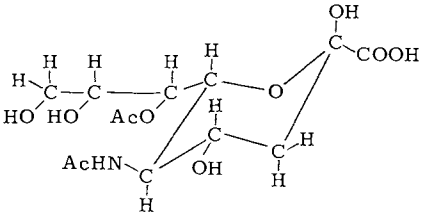


(7)

Fig. 6. *N*-Glycoloylneuraminic acid *(7)*.



(8)



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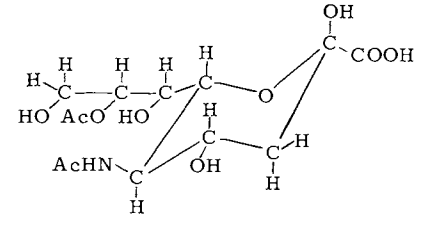

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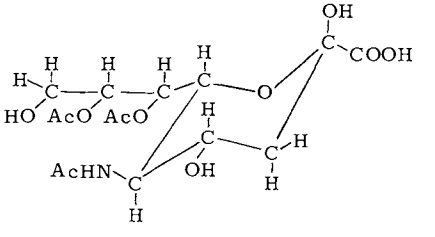


(11)

Fig. 7. Structural formulas of some *N*-acetyl-*O*-acetylneuraminic acids: *N*-acetyl-4-*O*-acetylneuraminic acid *(8)*, *N*-acetyl-7-*O*-acetylneuraminic acid *(9)*, *N*-acetyl-8-*O*-acetylneuraminic acid *(10)*, and *N*-acetyl-7,8-di-*O*-acetylneuraminic acid *(11)*.

Rich sources of *N*-acetyl-*O*-acetylneuraminic acids are bovine and horse submaxillary mucins, whose acylneuraminic acid fraction consists of 60—70% of *O*-acetylated *N*-acetylneuraminic acid. As shown in Table 1, the diacetylneuraminic acids from bovine submaxillary glycoprotein each contain one *O*-acetyl group in position 7 or 8 [*(9)* and *(10)*][8,40,67], whereas that of the corresponding horse glycoprotein is *O*-acetylated on C-4 [*(8)*] (Fig. 7)[8,40]. The positions of the two *O*-acetyl groups of bovine triacetylneuraminic acid *(11)* are known (Table 1), whereas the position of the second *O*-acetyl group in horse triacetylneuraminic acid[40] still remains to be established. A tetraacetylated neuraminic acid (*N*-acetyl-tri-*O*-acetylneuraminic acid[68]) has been isolated in small quantities from bovine submaxillary glycoprotein. *N*-Acetyl-*O*-acetylneuraminic acids also occur in other glycoproteins of animal[69] and of human origin[70] as well as in oligosaccharides, *e.g.*

Table 1. Composition of the acylneuraminic acid fraction of bovine and horse submaxillary mucins.—means not detectable (from Ref. [68]).

Acylneuraminic acid	Submaxillary mucin Bovine [%]	Horse [%]
N-glycoloylneuraminic acid *(7)*	15	1–2
N-acetylneuraminic acid *(1)*	20–25	15–20
N-acetyl-4-*O*-acetylneuraminic acid *(8)*	—	70–75
N-acetyl-7-*O*-acetylneuraminic acid *(9)*	*ca.* 25	—
N-acetyl-8-*O*-acetylneuraminic acid *(10)*	*ca.* 25	—
N-acetyl-7,8-di-*O*-acetylneuraminic acid *(11)*	5–10	—
N-acetyl-4,?-di-*O*-acetylneuraminic acid	—	2–5
N-acetyl-?-tri-*O*-acetylneuraminic acid	*ca.* 3	—

O-acetyllactaminolactose[71]. *Wiegandt*[72] isolated *N*-acetyl-8-*O*-acetylneuraminic acid *(10)* from gangliosides of the brains of several bony fishes.

The isomeric *N*-acetyl-*O*-acetylneuraminic acids behave differently from *N*-acetylneuraminic acid *(1)* in the periodic acid/thiobarbituric acid reaction; no difference is observed, on the other hand, in the orcinol/Fe^{3+} reaction. Whereas the 4-isomer *(8)* gives practically the same color yield as *(1)* with periodic acid/thiobarbituric acid, the molar extinction of the 8-isomer *(10)* is only 47% of that of *(1)*. The 7-isomer *(9)*, on the other hand, does not react at all with this reagent (Fig. 4), a fact that was reported and explained by *Paerels*[39].

The method that has proved best for the determination of the position of the *O*-acetyl groups is the polarographically followed periodic acid oxidation (Fig. 8). The fast consumption of periodic acid is 2 moles per mole of acylneuraminic acid if the three adjacent hydroxyl groups on C-7 to C-9 are unoccupied [*(1)* and *(8)*]; it is only 1 mole if the OH group on C-7 is esterified [*(9)*]. *(10)* no longer contains vicinal OH groups, as is shown by the particularly slow oxidation with periodic acid[40].

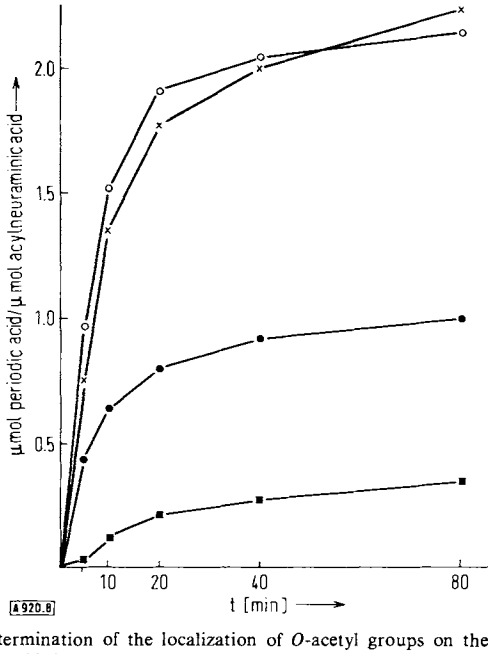


Fig. 8. Determination of the localization of *O*-acetyl groups on the neuraminic acid skeletons of several isomeric *N*-acetyl-mono-*O*-acetylneuraminic acids by polarographic measurement of the periodic acid consumption at 0 °C [40]. × — × *N*-Acetylneuraminic acid *(1)*; ○ — ○ *N*-acetyl-4-*O*-acetylneuraminic acid *(8)*; ● — ● *N*-acetyl-7-*O*-acetylneuraminic acid *(9)*; ■ — ■ *N*-acetyl-8-*O*-acetylneuraminic acid *(10)*.

Less common acylneuraminic acids are *N*-glycoloyl-8-*O*-methylneuraminic acid, which was found in the starfish *Asteria forbesi*[73], and *N*-(*O*-acetylglycoloyl)-4-methyl-4,9-dideoxyneuraminic acid (postulated structure), which was recently discovered in the egg membrane of the sea urchin[44]. *Hakomori* and *Saito*[74] have reported an *N*-glycoloyl-*O*-acetylneuraminic acid in glycosphingolipids of the membrane of horse erythrocytes, though they were unable to decide whether this was *N*-glycoloyl-4-*O*-acetylneuraminic acid or *N*-(*O*-acetylglycoloyl)neuraminic acid.

5. Synthetic Acylneuraminic Acids

The development of the synthesis of *N*-acetylneuraminic acid *(1)* from *N*-acetylglucosamine[14,15] or *N*-acetylmannosamine[75] and oxalacetate (Section 1) offered the possibility of preparing *N*-glycoloylneuraminic acid *(7)* and several *N*-acylneuraminic acids that do not occur in nature by the use of various *N*-acylated glucosamines or mannosamines (listed in Table 2). By the use of the derivatives of the above-mentioned coupling components introduced by *Kuhn* and *Baschang*[76] (4,6-benzylidene-*N*-acylglucosamine and di-*tert*-butyl oxalacetate), it was possible to obtain considerably higher yields of *N*-acylneuraminic acids (maximum 34%). A new method even gives *N*-acetyl- and *N*-glycoloylneuraminic acids in yields of 70—80%[48,25]. This method begins with the easily prepared methoxyneuraminic acid (see Section 3), which is *N*-acylated with acetic anhydride, *O*-carboxyglycolic anhydride (1,3-dioxolane-2,4-dione), or fluoroacetic or chloroacetic anhydride. The different *N*-acylneuraminic acids are liberated by subsequent glycoside cleavage in weakly acidic medium (Fig. 9, Table 2). This method is particularly suitable for the preparation of radioactively labeled *N*-[^{14}C, ^{3}H]acylneuraminic acids having high specific radioactivities, which are required for biochemical studies (Section 6).

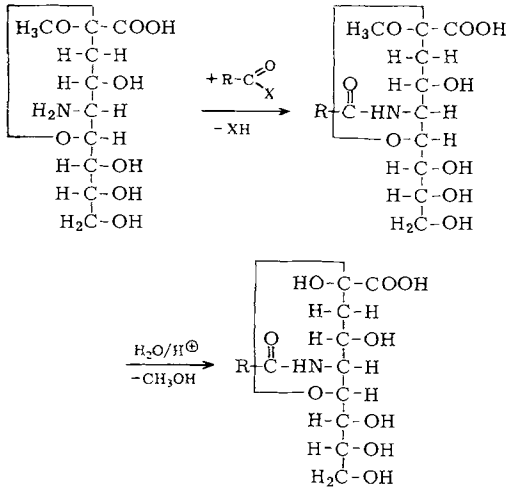


Fig. 9. Synthesis of *N*-acylneuraminic acids from neuraminic acid β-methylglycoside and acid anhydrides or acyl chlorides *via* *N*-acylneuraminic acid β-methylglycosides as intermediates.

Table 2. Synthetic *N*-acylneuraminic acids.

N-Acylneuraminic acid	Ref.
N-acetylneuraminic acid *(1)*	[14, 15, 48, 56, 75]
N-glycoloylneuraminic acid *(7)*	[25, 48, 77]
N-benzyloxycarbonylneuraminic acid	[78, 79]
N-ethoxycarbonylneuraminic acid	[79]
N-benzoylneuraminic acid	[79, 80]
N-propionylneuraminic acid	[80]
N-butyrylneuraminic acid	[80]
N-succinylneuraminic acid	[81]
N-formylneuraminic acid	[81]
N-chloroacetylneuraminic acid	[25]
N-fluoroacetylneuraminic acid	[25]

6. Biosynthesis of the Acylneuraminic Acids

The first enzymatic synthesis both of *N*-acetylneuraminic acid *(1)* and of *N*-glycoloylneuraminic acid *(7)* was achieved in good yields by *Comb* and *Roseman*[82] from pyruvate and *N*-acetyl-D-mannosamine or *N*-glycoloyl-D-mannosamine by a reversal of the aldol cleavage of acylneuraminic acids by acylneuraminate-pyruvate lyase, which was discovered by *Heimer* and *Mayer*[83], and which was described in Section 1 (Fig. 1). However, the biological function of this enzyme, which occurs in various bacteria and in mammalian organs, consists simply in the breakdown of free acylneuraminic acids (Section 7), and not in their biosynthesis. The bacterial and the mammalian organisms follow different paths for the synthesis of *N*-acetylneuraminic acid. The simpler path is followed *e.g.* in the bacterium *Neisseria meningitidis*[84], in which *N*-acetylneuraminate is formed in one step from *N*-acetyl-D-mannosamine and phosphoenol pyruvate:

$$\text{N-acetyl-D-mannosamine} + \text{phosphoenol pyruvate} + H_2O \xrightarrow{Mn^{2+},\ -SH} \text{N-acetylneuraminate} + \text{phosphate}$$

In the mammalian organism, on the other hand (see Fig. 10), this condensation must be preceded by phosphorylation of the acetylmannosamine by a specific kinase[85]. The resulting *N*-acetyl-D-mannosamine 6-phosphate reacts with phosphoenol pyruvate under the influence of the *N*-acetylneuraminate 9-phosphate synthetase, which has been concentrated from several organs (liver, submandibular gland)[86,87], to form *N*-acetylneuraminate 9-phosphate, which is then converted by a specific phosphatase[88] into free *N*-acetylneuraminate. These reactions, which have been observed in particle-free homogenates of rat liver[86], the colonic mucous membrane of the sheep[89], and submandibular glands[51], are preceded by the biosynthesis of *N*-acetylmannosamine from *N*-acetylglucosamine by epimerizing enzymes[90,91]. The *N*-acetylglucosamine is formed from D-glucosamine and acetyl-coenzyme A[92]. Close relationships are clearly visible here between the hexose metabolism and the neuraminic acid metabolism[93].

Activation of the glycoside hydroxyl group is necessary for the transfer of the *N*-acetylneuraminic acid to glycoproteins or gangliosides. This is effected by acid-glycoside linkage of the *N*-acetylneuraminic acid with a phosphoric acid residue of cytidine triphosphate with elimination of pyrophosphate (Fig. 10). The resulting cytidine-5′-monophospho-*N*-acetylneuraminic acid *(12)* (Fig. 11) was first found in *Escherichia coli*[94], and was later synthesized with the aid of an enzyme concentrated from pig submandi-

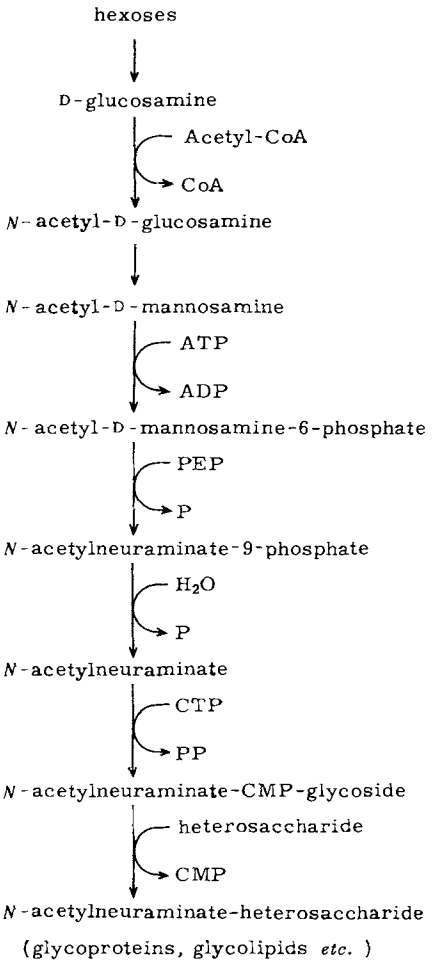
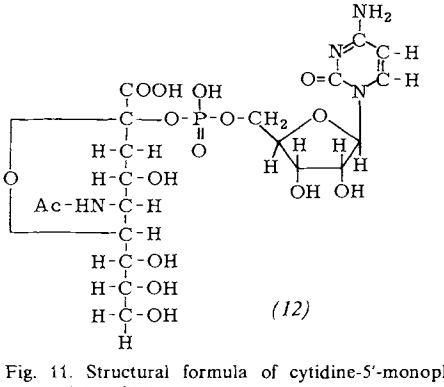


Fig. 10. Biosynthesis of *N*-acetylneuraminic acid ("*N*-acetylneuraminate") in mammalian tissues and glycoside linkage of the acid. Abbreviations: CoA = coenzyme A; ATP (ADP) = adenosine tri(di)-phosphate; PEP = phosphoenol pyruvate; P = inorganic phosphate; CTP (CMP) = cytidine tri(mono)phosphate; PP = pyrophosphate. (Scheme simplified up to *N*-acetyl-D-mannosamine.)

bular glands[95]. It is the substrate for sialyl transferases, *i.e.* enzymes responsible for the glycoside linkage of *N*-acetylneuraminic acid with other carbohydrates.

Sialyl transferases from various organs differ in their specificity with respect to the *N*-acetylneuraminic acid acceptor. Whereas a transferase from rat mammary glands transfers *N*-acetylneuraminate only to terminal β-galactopyranosyl groups of oligosaccharides, *e.g.* lactose[90], another sialyl transferase from the thyroid gland of the calf also links *N*-acetylneuraminate to galactose, but only if



(12)

Fig. 11. Structural formula of cytidine-5'-monophospho-*N*-acetylneuraminic acid *(12)*.

this is attached terminally to glycoproteins or glycopeptides (lactose is not an acceptor in this case[96]). In the submandibular gland of the sheep, *N*-acetylneuraminate is linked to *N*-acetylgalactosamine residues of the glycoproteins by another specific transferase, which, unlike the enzymes mentioned above, cannot transfer its substrate to galactose[97]. Further examples could easily be given.

Strict acceptor specificity for the hexoses or *N*-acetylhexosamines transferred by specific transferases is also observed throughout the biosynthesis of the oligosaccharide chain of glycoproteins. Thus according to the views of *Eylar*'s research group[99,98], the specificity of each glycosyl transferase for the sugar residue previously incorporated leads to a characteristic structure of the oligosaccharide component of a given glycoprotein, which can always be reproduced again. As assumed by *Gottschalk*[100], however, this acceptor specificity is not quite infallible, since the stepwise incorporation of the sugars, unlike in the synthesis of proteins, does not proceed by a gene-controlled template mechanism that substantially eliminates errors; the occasional incorporation of wrong carbohydrates can therefore lead to errors in the synthesis of the oligosaccharide chains of a given type of glycoprotein (microheterogeneity of the glycoproteins).

In contrast with *N*-acetylneuraminic acid *(1)*, the elucidation of the biosynthesis of *N*-glycoloylneuraminic acid *(7)* and of *N*-acetyl-*O*-acetylneuraminic acids was achieved only during the past five years. In agreement with an assumption first expressed by *Martensson et al.*[101], *N*-glycoloylneuraminic acid is formed directly from *N*-acetylneuraminic acid by oxidation[43,50,102,103]. By incubation of surviving slices of pig submandibular gland with [1-^{14}C]acetate and with several *N*-[1-^{14}C]acetylated precursors of *N*-acetylneuraminic acid and with $^{18}O_2$, it was possible to show that the *N*-glycoloyl group of *N*-glycoloylneuraminic acid is formed directly from the *N*-acetyl group by a hydroxylating enzyme[43,50,103] (Fig. 12). In addition to oxygen, this hydroxylation requires NADPH or ascorbate; in the presence of these cosubstrates, *N*-[1-^{14}C]-acetylneuraminate is converted in homogenates of pig submandibular gland into *N*-[1-^{14}C]glycoloylneuraminate, the reaction being brought about by an enzyme that is provisionally named as "*N*-acetylneuraminate, ascorbate, or NADPH : O_2 oxidoreductase (*N*-acetyl-hydroxylating)" (E.C. 1.14.1 or 2)[102].

N-Acetylneuraminic acid also functions as a precursor of *N*-acetyl-(oligo)-*O*-acetylneuraminic acids[51,68]. In bovine submandibular glands, acetyl groups are specifically transferred by acetyl-coenzyme A to the hydroxyl groups in positions 7 and/or 8 of *N*-acetylneuraminic acid, while *N*-acetyl-4-*O*-acetylneuraminic acid is formed in the corresponding gland of the horse. The experiments carried out both with surviving tissue slices and with homogenates show the existence of different position-specific *O*-acetyl transferases in both animals. These enzymes are called "acetyl-CoA : *N*-acetylneuraminate-7- and/or -8-*O*-acetyl transferase(s)" (bovine) and "acetyl-CoA : *N*-acetylneuraminate-4-*O*-acetyl transferase" (horse); (E.C. 2.3.1.?[51,68]).

The enzymes that hydroxylate or *O*-acetylate *N*-acetylneuraminic acid are largely bound on the subcellular

membranes ("microsomes") of the submandibular gland tissue[104, 105]. They belong there to a group of structure-bound enzymes that are responsible for the synthesis of the oligosaccharide chains of the glycoprotein produced in these glands. The chemical reactions of this "multi-enzyme complex" are illustrated for bovine submandibular gland (Fig. 13). The carbohydrate groups of bovine submandibular glycoprotein consist mainly of disaccharide

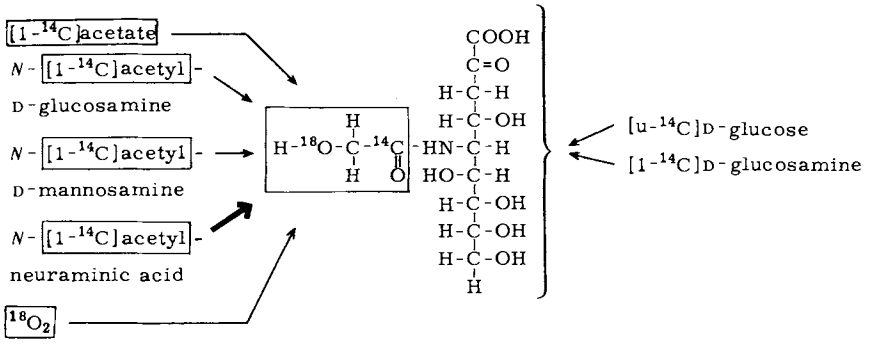


Fig. 12. Biosynthesis of *N*-glycoloylneuraminic acid *(7)* by direct oxidation of *N*-acetylneuraminic acid. The supply of radioactive acetate or of precursor substances of *N*-glycoloylneuraminic acid with *N*-[1-^{14}C]acetyl groups to surviving slices of pig submandibular gland leads to radioactive labeling only of the *N*-glycoloyl group of the neuraminic acid. $^{18}O_2$ is also incorporated specifically into the *N*-glycoloyl group, as evidence of the hydroxylation reaction. (On the other hand, the ^{14}C atoms of glucosamine or glucose can be detected after incubation both in the *N*-glycoloyl group and in the 9-C chain.)

units[106]. *N*-Acetyl-, *N*-glycoloyl-, or *N*-acetyl-(oligo)-*O*-acetylneuraminic acids (see Table 1) are bonded to *N*-acetylgalactosamine residues, which are linked to the peptide chain *via* serine or threonine[107]. In the biosynthesis of this glycoprotein (Fig. 13), *N*-acetylgalactosamine residues are first transferred by a specific *N*-acetylgalactosamine transferase[108] to protein chains, which are transported here from their ribosomal point of synthesis through "channels" of the endoplasmic reticulum (which can be isolated as a fraction of membrane-like particles that

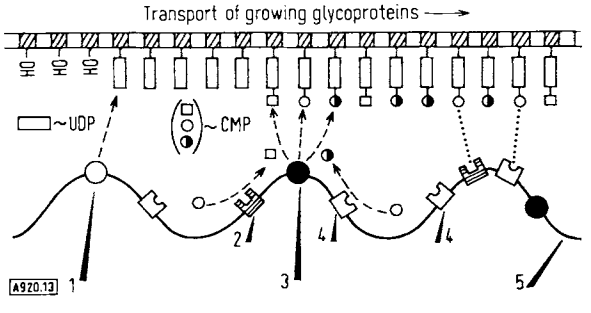


Fig. 13. "Multienzyme complex" in the subcellular membranes of bovine submandibular gland, which is responsible for the biosynthesis of the oligosaccharide part of the glycoprotein molecules of the submaxillary mucin. The proposed model is explained in the text. ○ *N*-Acetyl-, □ *N*-glycoloyl-, ◑ *N*-acetyl-7(8)-mono- and -di-*O*-acetylneuraminic acids: ▭ *N*-acetylgalactosamine; ▨ serine and threonine residues of the protein chain.
1: *N*-Acetylgalactosamine transferase, 2: *N*-acetylneuraminate, ascorbate, or NADPH: O_2-oxidoreductase; 3: sialyl transferase(s); 4: *N*-acetylneuraminate-7(8)-*O*-acetyl transferase(s); 5: subcellular membrane. (Abbreviations: CMP = cytidine monophosphate; UDP = uridine diphosphate; NADPH = reduced nicotinamide adenine dinucleotide phosphate.)

sediment at $10000 \times g$[105]). This is followed by the transfer (as cytidine monophosphate glycosides) of the *N*-acetylneuraminic acid and its (presumably on the membrane surface) hydroxylated or *O*-acetylated derivatives to the *N*-acetylgalactosamine residues; acylneuraminic acid-specific transferases have been suggested for this transfer[50, 51]. It is only now, as has been shown by experiments with microsomes labeled with *N*-[1-^{14}C]acetylneuraminic acid, that part of the *N*-acetylneuraminic acid molecules that have already been incorporated into the glycoprotein of the subcellular membrane are modified by the hydroxylase or *O*-acetyl transferase[104, 105, 109]. After the incorporation of the acylneuraminic acids, the completed glycoprotein is released from the membranes, stored in the cytosol[51, 109], and released as required by the salivary gland in a highly viscous solution.

In the described biosynthesis of bovine submandibular glycoprotein, we have seen a mechanism that appears to be of general validity in the biosynthesis of glycoproteins. After the completion of the protein part of the glycoproteins, the addition of the first sugars to form an oligosaccharide chain begins even on the ribosomes (in the "rough microsome" region)[110]. After its release from the ribosomes, the protein chain migrates to the region of the endoplasmic reticulum known as "smooth microsomes", where the oligosaccharide chain is built up further by transfer of hexoses or of their derivatives and completed by the attachment of acylneuraminic acids or even of fucose[98, 100, 111–115]. The specific glycosyl transferases responsible for the synthesis of the oligosaccharide portion of the glycoprotein are presumably parts of a multienzyme complex[99] that is situated in the smooth microsomes or in the Golgi apparatus[116].

7. Enzymatic Degradation of the Acylneuraminic Acids

Most acylneuraminic acids can be readily released from their α-ketoside (see Section 4) linkage to glycoproteins or gangliosides by an enzyme that *Gottschalk*[117] called "neuraminidase" (E.C. 3.2.1.18; suggested systematic name: "acylneuraminide-acylneuraminosyl hydrolase"[118]). This process introduces the degradation of the glycoproteins or gangliosides. Neuraminidase occurs widely in lysosomes of vertebrate organs[119–121] and in bacteria[122], and can be isolated and crystallized[41, 125] from culture filtrates of *Vibrio cholerae*[123] or *Clostridium perfrin-*

gens[124]. Neuraminidases also occur in some types of viruses ("myxoviruses"), *e.g.* in influenza viruses[126].

Comparative studies on the specificity of action of the neuraminidase from *Vibrio cholerae* have shown that the nature of the glycoside bonding partner of the neuraminic acid has much less influence on the ease of enzymatic cleavage of acylneuraminic acid glycosides than the size of the nitrogen substituent of the neuraminic acid or than chemical changes in the neuraminic acid in the vicinity of the glycoside linkage. Whereas synthetic glycosides of *N*-propionylneuraminic and of *N*-glycoloylneuraminic acids are more resistant to cleavage by neuraminidase than those of *N*-acetylneuraminic acid, the corresponding glycosides of *N*-benzyloxycarbonylneuraminic or *N*-butyrylneuraminic acid cannot be hydrolyzed by neuraminidase[127–129]. Esterification of the carboxyl group of the neuraminic acid blocks the action of neuraminidase completely[130], as does peracetylation of the molecule[127]. Partial *O*-acetylation of *N*-acetylneuraminic acid in positions 7 or 8, as *e.g.* in the diacetylneuraminic acids of bovine submandibular glycoprotein, reduces the rate of the hydrolytic liberation of these acylneuraminic acids by neuraminidase[40], as is shown by the fact that the Michaelis constant is greater than that of *N*-acetylneuraminic acid (Table 3). Esterification of the hydroxyl group on C-4 of *N*-acetylneuraminic acid with acetic acid even completely blocks the action of neuraminidase on the glycoside linkage (Table 3[40]). No experimental indications have been found so far for the part played by the (unoccupied) hydroxyl group on C-4 of the neuraminic acid in enzymatic catalysis by the neuraminidase. The biological significance of the resistance of *N*-acetyl-4-*O*-acetylneuraminic acid toward neuraminidase probably consists in protection of the glycoprotein molecules that contain this acylneuraminic acid against attack by neuraminidase and thus against the further breakdown by other glycosidases.

Table 3. Influence of the position of *O*-acetyl groups on the neuraminic acid skeleton in *N*-acetyl-mono-*O*-acetylneuraminic acid glycosides on the Michaelis constants of acylneuraminide-acylneuraminosyl hydrolase ("neuraminidase" from *Vibrio cholerae* [40]) and of acylneuraminate-pyruvate lyase ("neuraminic acid aldolase" from *Clostridium perfringens* [131]).

Acylneuraminic acid tested	Michaelis constants (K_M) [mmol/l]	
	Neuraminic acid aldolase	Neuraminidase [a]
N-acetylneuraminate	1.85	2.5
N-acetyl-8-*O*-acetylneuraminate	2.00	16.0
N-acetyl-7-*O*-acetylneuraminate	4.55	16.0
N-acetyl-4-*O*-acetylneuraminate	12.50	∞

[a] The acylneuraminic acids were bound to bovine or equine submaxillary glycoproteins.

The acylneuraminic acids released from their glycoside linkage are degraded by an aldolase, acylneuraminate-pyruvate lyase[131] (E.C. 4.1.3.3). This leads in reversible reactions to the formation of pyruvic acid and acylmannosamines, as was shown in Figure 1 for *N*-acetylneuraminic acid[132]. *O*-Acetyl groups sometimes also have a strong influence on this cleavage reaction. As can be seen from the K_M values given in Table 3, an *O*-acetyl group in position 8 has only an insignificant effect on the enzyme activity, whereas in position 7 it reduces the rate of cleavage by about 40%, and in position 4 by about 80%.

The investigations described were carried out with acylneuraminate-pyruvate lyase from *Clostridium perfringens*[131]. Like neuraminidase, the enzyme occurs widely; it has been detected in several bacteria and has also been isolated from mammalian organs (references can be found in[131, 133, 134]).—In the catalysis of the aldolase from *Clostridium perfringens* the participation of lysine residues forming intermediary Schiff bases between enzyme and substrate molecules and of histidine residues has been demonstrated[134].

8. Biological Functions of the Acylneuraminic Acids

The widespread occurrence of the acylneuraminic acids suggests that they are of great biological importance. A number of vital processes in which the acylneuraminic acids play a decisive part have indeed been found in recent years. Some examples are given below, grouped according to function (for reviews see Ref. [135]).

8.1 Increase in the Viscosity of Glycoproteins in Aqueous Solution ("Mucus")

Acylneuraminic acids bonded to glycoproteins are partly responsible for the high viscosity of mucilaginous secretions of the respiratory passages, the digestive tract, the urogenital tract, and the eye socket. Because of their low pK values (see Section 2), their carboxyl groups are largely dissociated at physiological pH values (approx. 7.4), so that the filamentous glycoprotein molecules are extended by abundant coverage with negatively charged, mutually repelling acylneuraminic acid residues. The result of this and of the very high molecular weight (up to several million) is a high viscosity of aqueous solutions of these neuraminic acid-rich glycoproteins, such as occur *e.g.* as secretions of mucous membranes[136].

The mucilaginous glycoprotein solutions are vital[135]. They act as lubricants for the rotation of the eyeball, and they prevent the cornea from drying out and protect it against damage by grains of dust *etc.* In the oral cavity and in the gastrointestinal tract, they envelop foods, so making them slippery and protecting the tender mucous membranes against mechanical and chemical (stomach acid, digestive enzymes, *etc.*) damage. The neuraminic acid in this way opposes the formation of stomach ulcers. The layer of mucin that is continuously transported outward on the epithelium of the respiratory passages moistens the air breathed, traps bacteria and other impurities in the air, some of which may be corrosive, and in this way keeps the lungs sterile. Similarly, a very viscous plug of mucin in the cervical canal of the uterus keeps bacteria out of the uterine cavity, and hence out of the abdominal cavity. This viscosity barrier is lowered only at the time of ovulation to admit spermatozoa. Glycoproteins rich in neuraminic acid that are secreted by mucous glands of the vagina are important to reproduction in that they facilitate both coitus and childbirth[135].

8.2. Further Functions in Reproduction

Neuraminic acid is also directly involved in the formation of a sperm reservoir in the vagina of the pig that guarantees fertilization. The ejaculum of the boar contains a high molecular weight, acidic glycoprotein (isoelectric point: pH = 1.1) containing 25% of *N*-acetylneuraminic acid, which agglutinates with a basic protein to form a network from which the spermatozoa are released over a long period[137]. Glycoproteins rich in neuraminic acid, which are known as "fertilisin", are present in the egg membranes of some animals, *e.g.* sea urchins[138], that are deposited in the water, and these glycoproteins specifically bind spermatozoa. Neuraminic acid plays a decisive role here, and allows reliable fertilization. Neuraminic acid also appears to be essential to fertilization as a component of the zona pellucida of the egg cells of mammals: after enzymatic removal of the acylneuraminic acid, the egg cell of the rabbit loses its elasticity, and spermatozoa can no longer penetrate into it[139].

8.3. Binding and Transport of Molecules and Viruses

Some types of virus can attach themselves to cells with the aid of cell-membrane-bound acylneuraminic acids. Red blood cells are agglutinated by myxoviruses[140], which include a number of types that are pathogenic to animals or to man, *e.g.* influenza viruses[32, 141, 142]. This "hemagglutination" is due to the neuraminidase, the only enzyme of these viruses, and presumably to a second specific virus protein, hemagglutinin[142], which, because of a high affinity for neuraminic acid, allow the adsorption of viruses on the erythrocytes and hence permit their agglutination. Erythrocytes treated with neuraminidase no longer exhibit this phenomenon. (In human erythrocyte membranes, part of the *N*-acetylneuraminic acid that serves as the virus receptor is a constituent of M and N blood-group substances[143].) It has been suggested[142, 144] that the cell neuraminic acid plays a part, which is not yet entirely understood, in the infection of cells with myxoviruses.

Acylneuraminic acids bound on the surface of cells are involved in the transport of potassium through cell membranes[145], and act in smooth muscle as receptors for the stimulating substance serotonin[146]. Plasmapexin, a neuraminosyl glycoprotein of blood plasma, binds the base histamine[147].

8.4. Effects on Surface Charge, Aggregation, and Shape of Cells

Negatively charged acylneuraminic acid residues impart a certain strength[148] to cell membranes because of their mutual repulsion, and influence the mutual adhesion of cells in the organ structure. Whereas neuraminic acid allows the aggregation of embryonal muscle cells of the hen, presumably *via* Ca^{2+} bridges[149], it prevents spontaneous clumping of blood platelets[150, 151], and so opposes any undesirable formation of blood clots.

8.5. Protection of Macromolecules against Proteolytic Attack

N-Acetylneuraminic acid protects the "intrinsic factor", a neuraminic acid glycoprotein secreted by the mucous membrane of the stomach, against the action of proteolytic enzymes. The intrinsic factor binds vitamin B_{12} ingested with the food and allows its absorption in the lower sections of the intestine. As was shown by *Faillard* and *Pribilla*, the intrinsic factor still retains its ability to bind vitamin B_{12} after removal of the neuraminic acid, but the absorption of the vitamin from the intestinal lumen is no longer possible[152, 153]. This loss of the biological function in the intestine is due to destruction of the neuraminic acid-free intrinsic factor by proteolytic enzymes on the way to the absorption sites for vitamin B_{12}, which can be readily demonstrated in the test tube. *N*-Acetylneuraminic acid probably protects the intrinsic factor against the proteolytic destruction only because of its relatively strongly acidic carboxyl group, since replacement of *N*-acetylneuraminic acid by polyacrylic acid vinylpyrrolidine, which is also a strong acid, prevents the rapid breakdown of the neuraminic acid-free intrinsic factor by trypsin.

Free *N*-acetylneuraminic and *N*-glycoloylneuraminic acids have an inhibitory action on the fibrinolytic enzyme plasmin, and thus delay the dissolution of fibrin and the dangerous release of blood clots[154].

8.6. Regulation of the "Normal" Behavior and of the Lifetime of Cells and Macromolecules

The rate of the invasive growth of cancer tissue also appears to be influenced by the neuraminic acid content of the cell surface. The rate at which mouse tumor cells spread in tissue cultures is greatly reduced by removal of the neuraminic acid[155]. Neuraminic acid bound on the cell membrane protects erythrocytes against rapid phagocytosis by macrophages[156]. *N*-Acetylneuraminic acid protects macromolecules occurring in blood plasma, such as α_1-glycoprotein, ceruloplasmin, haptoglobulin, lactoferrin, human chorionic gonadotropin, and follicle-stimulating hormone, from a similar fate. These glycoproteins, which have important biological functions, are rapidly removed from the blood stream by liver parenchyma cells after loss of the acylneuraminic acid[157]. The glycoproteins mentioned are adsorbed by plasma membranes of the liver cells after removal of the acylneuraminic acid[158], and are probably withdrawn from the blood stream in this way. However, this binding is possible only if the plasma membranes themselves contain acylneuraminic acids.

It may be assumed that the neuraminic acid in erythropoietin, which stimulates the formation of red blood corpuscles in the bone marrow, has a similar action in the blood circulation. Thus it has been shown that *N*-acetylneuraminic acid must remain bound to the erythropoietin if it is to exert its biological action after injection into the blood stream in the intact animal[159]; on the other hand, no *N*-acetylneuraminic acid is required for the action of the hormone in bone marrow cell cultures[160].

Neuraminic acid on the surface of lymphocytes regulates the normal distribution of these cells in the body, though the manner in which it does this is not yet known. After loss of the neuraminic acid, the cells are not accumulated in the normal manner in the lymph nodes or in the spleen, but in the liver[161].

8.7. Masking of Cellular Antigens

An observation that is probably of great biological importance is that acylneuraminic acids of the cell membranes reduce the immunochemical reactions both of healthy and of carcinomatously degenerated cells[162, 163]. A fetus in the uterine cavity, for example, is immunologically speaking a foreign body (a "transplant") as far as the mother is concerned, since the composition of its proteins is also determined by the father. A histochemically detectable glycoprotein layer on the surface of trophoblast cells, the boundary zone between mother and child, may form an immunobarrier between the two organisms, which prevents the mother from producing antibodies against the child. This assumption is based on the observation that antibodies against mouse trophoblast cells can be formed in the mother mouse only after enzymatic removal of the acylneuraminic acid from the surface of these cells. As a result of this treatment, the tissue of young animals (tested with skin transplants) is no longer tolerated by the mother organism, but is rejected[164].

If methylcholanthrene-induced mouse sarcoma cells are treated with neuraminidase and then injected into hereditarily equal mice, antibodies that prevent the development of massive tumors are formed (without this removal of neuraminic acid, reliably fatal tumors are formed[165]). Similar observations have been made with leukemia cells[166] and with Landschütz ascites tumor cells[167] in mice. Whether this phenomenon can be used for cancer therapy in man is still the subject of speculation.

Whereas some of the effects of acylneuraminic acids described here, *e.g.* the increase in viscosity, the binding of bases, and in part also protection against proteases, can be explained by their physical properties, particularly the negative charge, there are as yet no satisfactory explanations for many other biological effects of acylneuraminic acids that have been mentioned here.

It is not yet known why so many enzymes are acylneuraminosyl glycoproteins[32, 168]. It is interesting to note that hydrolases in particular, *e.g.* phosphatases from lysosomes of mammals, contain neuraminic acid, which imparts electronegativity to the enzyme molecules. (The electrophoretic mobility of these enzymes is therefore considerably altered on removal of the neuraminic acid[169, 170]). The enhanced resistance of these enzymes to proteolytic decomposition is attributed, as in the case of the intrinsic factor, to the presence of acylneuraminic acid residues[170]. Apart from the acidic phosphatase from the human prostate, which exhibits a slight increase both in the pH optimum of the enzyme activity and in the affinity for the substrate on loss of the neuraminic acid[171], no effects of the bound acylneuraminic acids on the enzyme activity have so far been found.

There is also still speculation regarding the part played by the acylneuraminic acids as well as by the other carbohydrate components in many other biologically important glycoproteins[135], *e.g.* immunoglobulins, basal membranes (these have supporting functions for cells in the organ or filtration functions as in the glomeruli of the kidney[172]), glycoproteins and gangliosides of the nerve tissue (these are mainly localized on particular elements such as microsomes and synaptosomes and maybe involved in the conduction of stimuli or even in the memory function of the brain[173, 174]), metal ion-binding glycoproteins of the blood and of the bone tissue, hormone-transporting macromolecules and protease inhibitors of the blood plasma, and components of the blood clotting system.

There is no doubt that it would be worthwhile to push ahead with the explanation of all functions of the *N*-acetyl-, *N*-glycoloyl-, and *N*-acetyl-*O*-acetylneuraminic acids that are structural elements of molecules from very diverse sources and with such different biological tasks. The same is true of the structure and function of the carbohydrate components to which the acylneuraminic acids are bound in these molecules.

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Chemistry and Biochemistry of Azaquinones

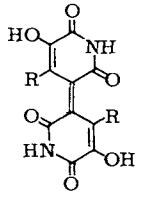
By Hans-Joachim Knackmuss[*]

The azaquinones are a new class of bacterial secondary metabolites. Investigations were necessary on the chemistry of the azaquinones, their imides, and 2,3,6-pyridinetriols and 3-aminopyridine-2,6-diols in order to obtain information about the structure and biogenesis of these natural products.

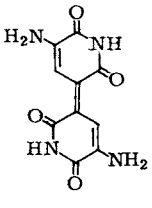
1. Occurrence of Azaquinones

Most bacteria are colorless, but species are occasionally observed having yellow to orange, or less frequently red and violet pigments. Blue bacterial pigments are a rarity. The earliest known was the blue phenazine pigment pyocyanine from *Pseudomonas aeruginosa* and *Cyanococcus chromospirans*. Bacterial indigotin is formed by *Pseudomonas indoloxidans* on nutrients containing indole.

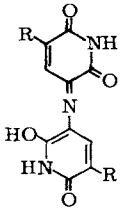
Azaquinonoid structures have recently become accepted for a group of blue bacterial pigments. With pyridinols as carbon and nitrogen sources, it is easy to grow bacteria that partly oxidize the substrate to blue pigments. The pigment deposited in large crystals by *Arthrobacter crystallopoietes* has the diazadiphenoquinone structure *(1)*[1]. A pigment formed by bacterial oxidation of isonicotinic acid or 2,6-dihydroxyisonicotinic acid is reported to have a similar structure *(2)*[2].



(1), R = H
(2), R = CO_2H



(3)



(4), R = Ribosyl
(5), R = Octanoylamino

The formation of blue, presumably azaquinonoid pigments is observed in the degradation of nicotine and of nicotinic acid by species of *Arthrobacter* and of *Pseudomonas*[3]. A component of the nicotine blue from *A. oxidans* was recently obtained in the crystalline state[4] and recognized as the monopotassium salt of *(1)*[24,25][**].

The extracellularly formed diazadiphenoquinone indigoidine *(3)* is obtainable in fairly large quantities from cultures of *Corynebacterium insidiosum*, *Pseudomonas indigofera*, *Arthrobacter atrocyaneus*, and *Arthrobacter polychromogenes* (see Section 3.1)[1]. Small quantities of *(3)* have been detected in three plant-pathogenic strains of bacteria of the *Erwinia chrysanthemi* group[5].

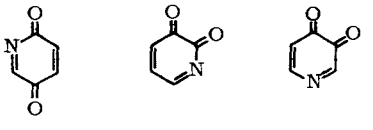
In addition to the water-insoluble indigoidine *(3)*, *Arthrobacter polychromogenes* excretes a water-soluble azaquinone, indochrome *(4)*[6]. Both pigments have also been identified in cultures of two *Arthrobacter* species, two *Corynebacteria*, and *Micrococcus flavocyanus*[7]. As early as 1900, a soluble pigment having the properties of indochrome was described, together with "colored, insoluble crystals", for a bacterium called *Bacillus polychromogenes*[8]. Indochrome consists of several components, which differ in linkage and configurations of the ribosyl residues (see Section 3.2).

The intracellularly formed blue pigment *(5)* of *Pseudomonas lemonnieri*, like indochrome, has a diazaindophenol structure[9] (see Section 3.3).

2. Formation and Reactions of the Azaquinones

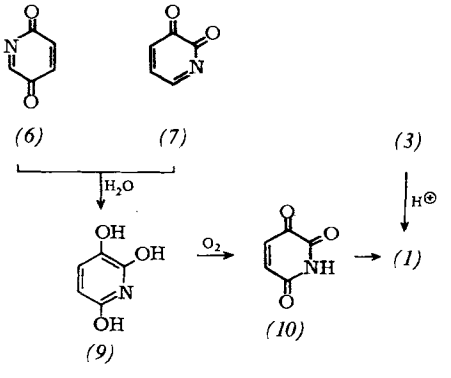
2.1. Azabenzoquinones and Their Solvation

The three isomeric azaquinones *(6)*, *(7)*, and *(8)* are formally derived from *p*- and *o*-benzoquinone by replacement of CH by N. The "pyridoquinone" having the structure



(6) *(7)* *(8)*

(6) or *(7)* described as an oxidation product of pyridinediols[10] was later found to be diazadiphenoquinone *(1)*[11]. The azaquinone *(6)* or *(7)* formed as the primary



(6) *(7)* *(3)* *(9)* *(10)* *(1)*

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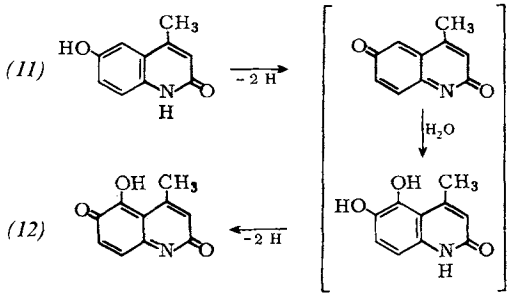
[**] *Note added in proof:* The second labile component of nicotine blue has now been isolated as a barium salt. Spectroscopic data indicate a structure similar to *(1)*, where one OH group is replaced by H.

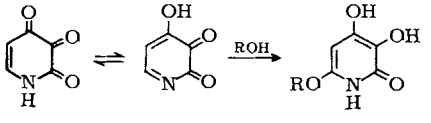
product on oxidation of 2,5- or 2,3-pyridinediol[10] or of 5- or 3-amino-2-pyridinol in strongly acidic solution[12] undergoes hydration at the C=N bond to form 2,3,6-pyridinetriol *(9)*[*]. Further oxidation leads to 2,3,6-trioxo-1,2,3,6-tetrahydropyridine *(10)*[**], which dimerizes to *(1)*.

Hydration at the C=N bond is not possible when 6-hydroxy-4-methyl-2-quinolone *(11)* is oxidized[13]. Water is added instead to the carbocyclic quinonoid ring of the intermediate. Further oxidation then leads to the azanaphthoquinone *(12)*.

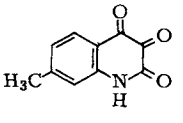
The azaquinone pyromekazone [*(13a)*⇄*(13b)*] crystallizes as colorless needles which always contain 1 mole of alcohol of crystallization [as *(13c)*][14]. Here again, solvation must have occurred at the C=N bond of the tautomer *(13b)*. On the other hand, the yellow benzo homolog



(14)[15] cannot be correspondingly solvated.



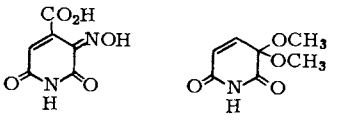
(13a) *(13b)* *(13c)*



(14)

2.2. Dimerization of 2,3,6-Trioxo-1,2,3,6-tetrahydropyridine

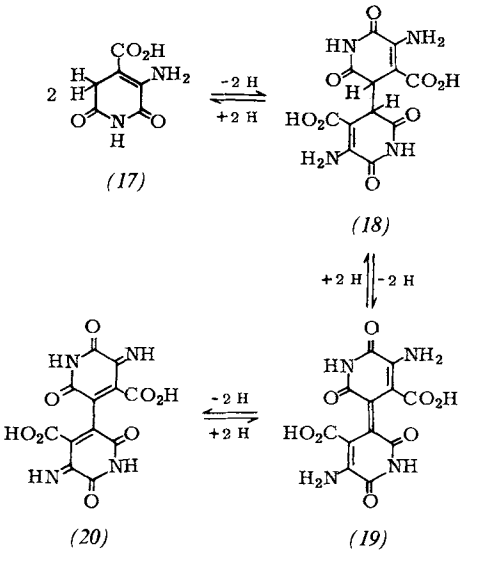
The oxidation of 2,3,6-pyridinetriols or 3-amino-2,6-pyridinediols always leads to dimers if position 5 is free. An example is the dimerization of *(10)* with formation of *(1)*. The formation of *(1)* from *(15)*[16] or *(16)*[17] on acid hydrolysis can be explained in the same way.



(15) *(16)*

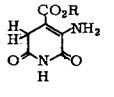
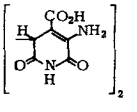
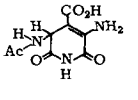
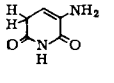
2.3. Oxidation Products of 3-Amino-2,6-pyridinediols

The oxidation of aminocitrazinic acid *(17)*[18], which can be followed potentiometrically, can be described by Scheme 1[19]. Like the blue indigoidinedicarboxylic acid *(19)*[11], the colorless oxidation products, the bipyridyl



Scheme 1. Reversible oxidation of aminocitrazinic acid *(17)*.

Table 1. UV-spectroscopic data for some 3-amino-2,6-pyridinediol derivatives.

Compound		λ_{max} [nm] in CH_3OH	log ε
	*(17)*, R = H	329	3.83
	(17a), R = CH_3 [a]	328	3.91
	*(18)*	332	4.04
	*(55b)*	328	3.82
	*(21)*	320	[b]

[a] NMR spectrum in D_6-dimethyl sulfoxide: τ = −2.50 (NH or OH); 3.03 (NH_2); 6.60, 6.30 (CH_2, CH_3).
[b] Determined for the hydrochloride after addition of Dowex 2×4 (OH^- form).

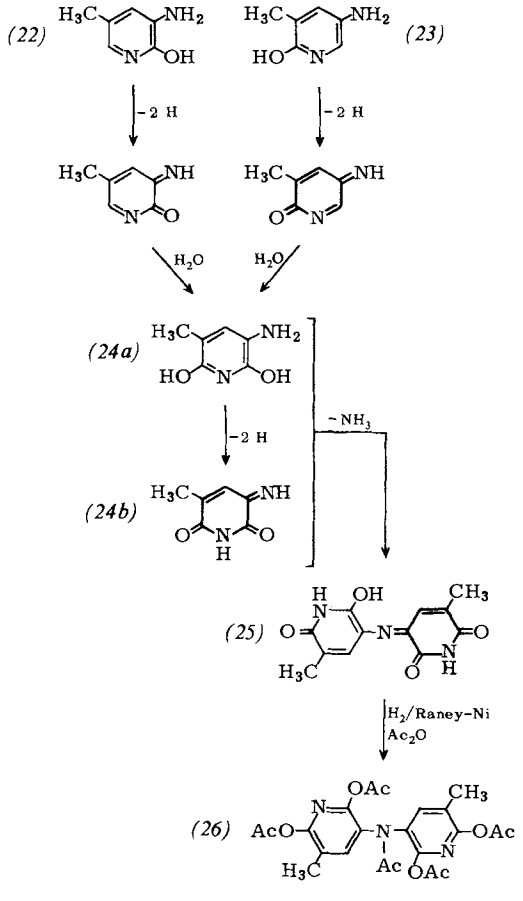
[*] 2,3,6-Pyridinetriol *(9)* actually exists, at least in DMSO, as an equilibrium mixture of 3-hydroxy-2,6-dioxo-1,2,5,6-tetrahydropyridine *(9a)* and 3,6-dihydroxy-2-pyridone *(9n)* (sse Section 2.5).

[**] Because of the easy solvation of the —CH=N group, only azaquinones in which the carbon atoms adjacent to the nitrogen are substituted by oxygen are known. In the present work, these azaquinones were represented in the tautomeric imide form (as 2,3,6-trioxo-1,2,3,6-tetrahydropyridines), as in formula *(10)*. According to their IR spectra, the azaquinones appear to exist largely in this form. However, the simple compounds *(30)*, *(31)*, *(36)*, and *(27)* in particular have electronic spectra typical of benzoquinones, from which the azaquinones are formally derived by replacement of a —CH=CH by a —CO—NH group (see Section 2.5).

derivative *(18)* and the bis(azaquinone imide) *(20)* can also be isolated in the pure form; their constitution has been confirmed by spectra[19] (cf. Table 1). All oxidation steps, and also the transition *(17)*⇄*(18)* at a suitable pH, can be reversed by hydrogenation (with Raney nickel)[19]. Corresponding to the formation of *(19)*, indigoidine *(3)* is formed quantitatively by autoxidation of 2-amino-glutaconimide *(21)*[20].

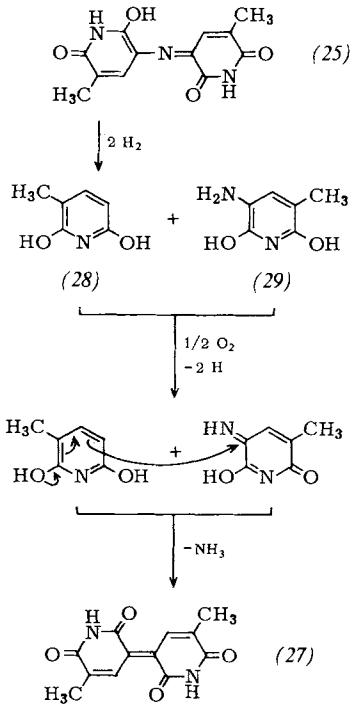
2.4. Azaquinone Imides

The oxidation of 5-substituted 3-amino-2-pyridinols or 3-substituted 5-amino-2-pyridinols, *e.g. (22)* or *(23)*, does not lead to azaquinhydrones[12] as was formerly assumed; the azaquinone imide *(24b)* formed as an intermediate is stabilized instead by condensation to form the diazaindophenol dye *(25)* corresponding to Scheme 2[21]. The dipyridylamine derivative *(26)* is formed by hydrogenation in acetic anhydride.



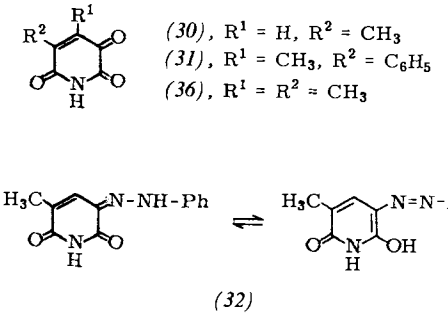
Scheme 2. Oxidation of 3- and 5-amino-2-pyridinols of the types *(22)* and *(23)*.

On hydrogenation of the dye *(25)* with Pd catalysts, *two* equivalents of H_2 are consumed. Autoxidation does not regenerate the diazaindophenol dye *(25)*; the diazadiphenoquinone *(27)* is formed instead. By trapping of the hydrogenolysis products [*(28)* as the 3-benzeneazoderivative and *(29)* as the tetraacetyl derivative], it was possible to verify the reaction represented in Scheme 3.



Scheme 3. Transformation of diazaindophenols of type *(25)* into diazadiphenoquinones of type *(27)*.

Concentrated nitric acid splits *(25)* into 5-methyl-2,3,6-trioxo-1,2,3,6-tetrahydropyridine *(30)*, which, like the homolog *(31)* described earlier[22], cannot dimerize



because of the substitution on C-5. *(30)* reacts with phenylhydrazine to form *(32)*, which is identical with the benzeneazo derivative of *(28)*.

2.5. Azaquinones from 2,3,6-Pyridinetriols

The products formerly referred to as "2,3,6-pyridinetriols"[23], which were formed by autoxidation, are shown by their absorption spectra to be homologs of the azaquinone *(30)*. The first true 2,3,6-pyridinetriols are the four recently synthesized homologs *(9)*, *(33)*, *(34)*, and *(35)*[24,25] (Table 2).

To avoid autoxidation, the synthesis was always directed toward the 2,3,6-triacetoxy derivatives. These can be hydrolyzed in concentrated hydrochloric acid in the

absence of O_2 to the hydrochlorides of the pyridinetriols, which readily lose HCl at high temperatures with sublimation of the free bases.

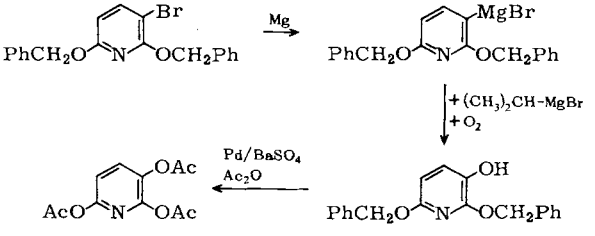
Table 2. Tautomeric equilibria of the 2,3,6-pyridinetriols in dimethyl sulfoxide.

	R^1	R^2	K_T [a]
(9)	H	H	1.75
(33)	H	CH_3	0.4
(34)	CH_3	CH_3	2.0
(35)	CH_3	H	4.2

(a) ⇌ *(b)*

[a] $K_T=[(a)]/[(b)]$.

The triacetyl derivative of *(33)* is readily obtained by hydrogenative acetylation of *(30)*. The corresponding derivatives of *(34)* and *(35)* are obtainable by hydrolysis and subsequent acetylation of the 3-diacetylamino-2,6-diacetoxypyridines. 2,3,6-Triacetoxypyridine itself was unobtainable by an analogous path, and was synthesized in accordance with Scheme 4[25].



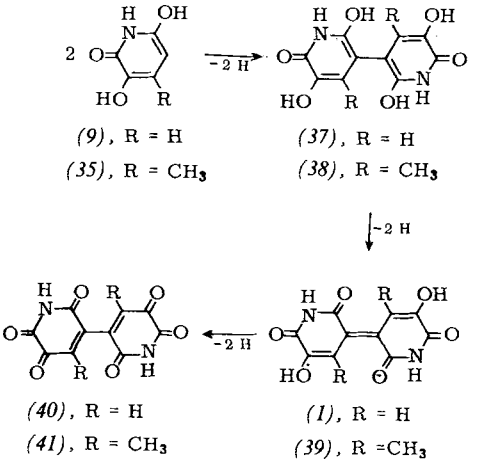
Scheme 4. Synthesis of 2,3,6-triacetoxypyridine.

The sublimed 2,3,6-pyridinetriols contain two oxo groups, corresponding to the formulas *(9a)*, *(33a)*, *(34a)*, and *(35a)*. On dissolution, these forms set up an equilibrium with the OH forms *(b)*, and this process can be followed by UV and NMR spectrometry. The K_T values given in Table 2 were determined by NMR spectroscopy. Similar values are calculated from the UV spectra in methanol. In trifluoroacetic acid and in aqueous mineral acids, the equilibrium is strongly displaced in favor of the more basic OH form *(b)*. A form having three free OH groups is unknown.

In non-acidic solution, *e.g.* in methanol, the 2,3,6-pyridinetriols are autoxidized (their OH forms *(b)* particularly readily) to azaquinones. The reactions of *(33)* and of *(34)*, in which the CH_3 groups on C-5 hinder dimerization, lead quantitatively to the monomeric azaquinones *(30)* and *(36)* respectively.

In the autoxidation of *(9)* and *(35)*, dimerization can take place *via* position 5 (see Scheme 5). The final reaction products are the bis(azaquinones) *(40)* and *(41)*. Depending on the reaction conditions chosen, it is possible to intercept the intermediates of the oxidation. Unlike the indigoidine hydrolysis product *(1)*, the diazadiphenoquinone *(39)* is unstable because of the steric hindrance of the CH_3 groups, and disproportionates into *(38)* and *(41)*.

The 2,3,6-trioxo-1,2,3,6-tetrahydropyridine structures formulated for the azaquinones *(30)*, *(31)*, *(36)*, *(40)*, and *(41)* have been confirmed by comparison of the IR spectra



Scheme 5. Autoxidation of 2,3,6-pyridinetriols.

(medium-strong carbonyl absorption at 1730 to 1745 cm^{-1}). The corresponding structure for *(30)* was verified by recording the spectrum in solution. The straw-yellow compounds (in methanol) give a typical absorption spectrum of the type found for corresponding *p*-benzoquinones, which result on replacement of —CO—NH— by —CH=CH—.

3. Azaquinones from Bacteria

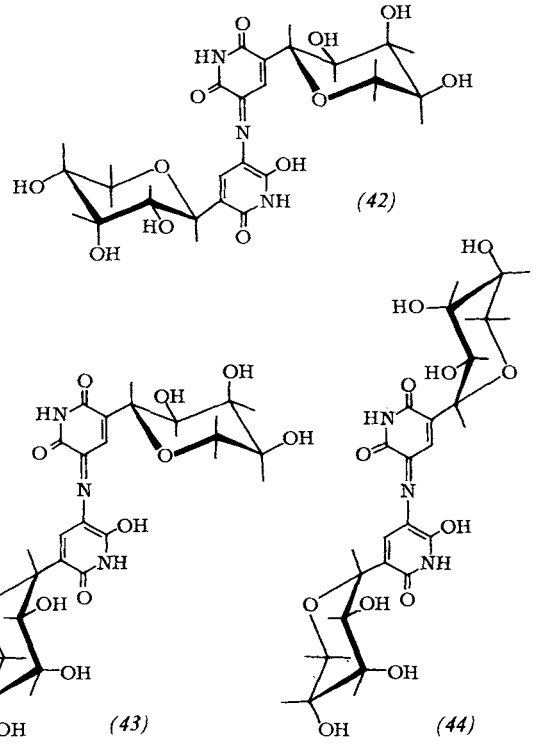
3.1. Indigoidine

Indigoidine *(3)* owes its name to its indigo-like color and vat dyeing properties. In solution and in the vat, the bacterial pigment undergoes slow partial loss of the exocyclic nitrogen, and this hindered the elucidation of the structure of the pigment, which was observed as early as 1890[26]. The decisive step in the determination of the structure was the degradation of indigoidine to the soluble bis(azaquinone) *(40)* by hydrolysis [*(3)*→*(1)*] followed by dehydrogenation with nitric acid[11]. Many syntheses have been described for the degradation products and for the pigment itself[11,20]. The synthesis of indigoidinedicarboxylic acid *(19)* and its decarboxylation to *(3)* also prove the structure of the bacterial pigment.

3.2. Indochrome

The water-soluble blue indochrome is released into the culture liquid only by indigoidine-producing bacteria. In addition to a biogenetic relationship, a structural relationship also had to be assumed between the two pigments. Indochrome consists of at least five isomeric pigments, the

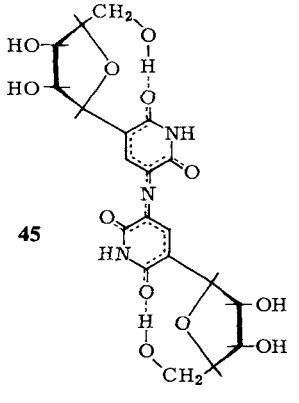
main components of which have been separated chromatographically. The structure *(42)* has been accepted for the



(42)

(43)

(44)

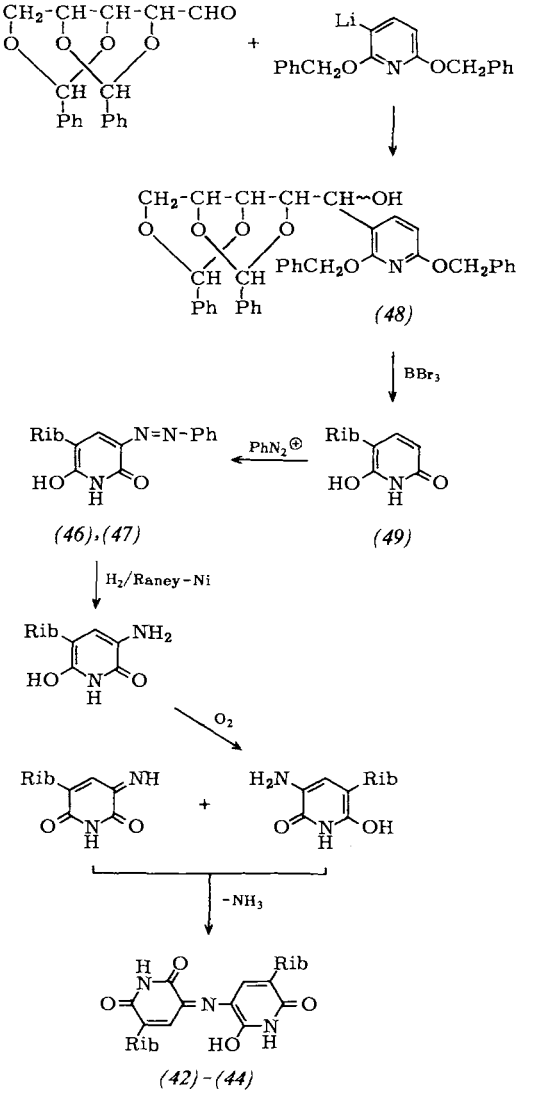


45

Indochrome A: *(42)*
Indochrome B I: *(43)* + *(44)*
Indochrome B II: *(45)*
Indochrome B III: contains the α-D-ribofuranosyl residue

dye acid of indochrome A, and the structure *(45)* for indochrome B II. The pigment component B I consists mainly of *(43)*, and contains small quantities of *(44)*. The minor indochrome component B III and other very weak chromatographic zones are thought to contain the thermodynamically little favored α-D-ribofuranosyl residue. On equilibration in trifluoroacetic acid, the pure pigment components regenerate the natural isomeric mixture. Indochrome is thus an equilibrium mixture. The structures of the components have been determined by UV, ORD, and NMR spectra and by degradation and synthesis[6,27]. Corresponding to the degradation of *(25)* to *(32)*, degradation of indochrome A *(42)* with nitric acid followed by condensation with phenylhydrazine yields *(46)*. From indochrome B I [*(43)* + *(44)*] the α-anomer *(47)* is obtained in addition to *(46)*.

The phenylhydrazones *(46)* and *(47)* were prepared as indicated in Scheme 6. The alcohol *(48)* obtained by condensation has been resolved into its isomers. "Deazauridine" *(49)*[28] was obtainable as an isomeric mixture by ether cleavage with BBr_3, and pure *(46)* and *(47)* were obtained by coupling with benzenediazonium chloride. Hydrogenation and autoxidation of *(46)* and *(47)* lead smoothly to indochromes, *(46)* giving indochrome A [*(42)*], and an equimolar mixture of *(46)* and *(47)* giving indochrome A *(42)* and indochrome B I [*(43)* + *(44)*] [*(42)* : *(43)* : *(44)* = 1 : 2 : 1]. If an equilibrium mixture of 3-D-ribosyl-5-benzeneazo-3,6-pyridinediol (*e.g.* a precipitated crude product that also contains the ribofuranosyls) is used instead of the pure anomers *(46)* and *(47)* for the



(48)

(46), *(47)*

(49)

(42) - *(44)*

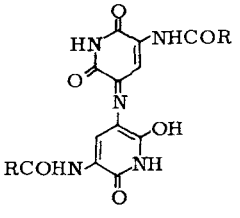
Scheme 6. Synthesis of the indochrome components *(42)* to *(44)*. *(42)* and *(46)*, Rib = β-D-ribopyranosyl; *(44)* and *(47)*, Rib = α-D-ribopyranosyl; *(43)*, Rib = α- and β-D-ribopyranosyl.

indochrome synthesis, one obtains a mixture of dyes that corresponds to the composition of natural indochrome and in which the indochromes B II and B III can also be detected. The presence of two identical α-D-ribofuranosyl residues

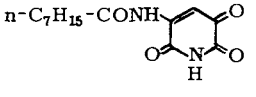
in indochrome B II is shown by the absorption and ORD spectra. The particularly deep blue color of indochrome B II in weakly basic solutions is explained, as shown earlier by the extended formula *(45)*, by strong intramolecular hydrogen bonding, which additionally stabilizes the mesomeric anion. The fixation of the chromophore plane with respect to the optically active center causes an unusually strong (multiple) Cotton effect (in DMSO).

3.3. The Pigment from *Pseudomonas lemonnieri*

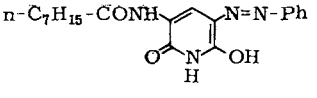
On the basis of spectral properties, degradation reactions, and syntheses, the structure *(50)* has been accepted for the dye acid of the pigment from *P. lemonnieri*[9,29]. The anion of *(50a)* is responsible for the deep blue color of the cells; the cation is unknown.



(50a), R = n-C_7H_{15}
(50b), R = CH_3



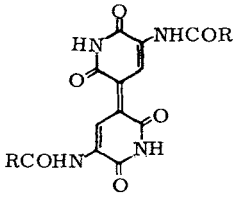
(51)



(52)

Corresponding to the degradation *(25)*→*(30)*, cold nitric acid degrades *(50a)* to the azaquinone *(51)*, which is stabilized by condensation with phenylhydrazine to form *(52)*.

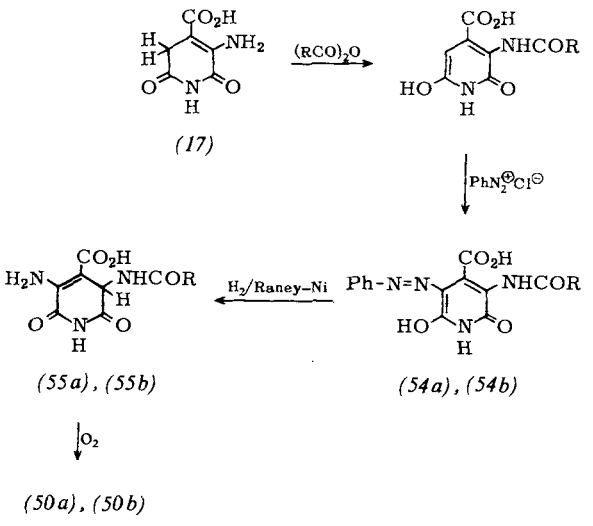
(50a) undergoes cleavage similar to that outlined in Scheme 3 on hydrogenation with Pd. Autoxidation yields *(53a)*, a homolog of diacetylindigoidine *(53b)*[1,11].



(53a), R = n-C_7H_{15}
(53b), R = CH_3

The structure of the pigment *(50a)* has been proved by synthesis of the homologous dye *(50b)* and of the pigment itself (see Scheme 7).

Acetylation or octanoylation of aminocitrazinic acid *(17)* followed by coupling with benzenediazonium chloride leads to the azo dye *(54b)* or *(54a)*. Sublimation of *(54a)* yields the phenylhydrazone *(52)*. The aminoacylaminocitrazinic acids *(55b)* and *(55a)* are obtained by hydrogenation, and readily undergo autoxidation to form *(50b)* and *(50a)* respectively. The model dye *(50b)* exhibits all the typical reactions of the bacterial dye



(17)

(55a), *(55b)*

(54a), *(54b)*

(50a), *(50b)*

Scheme 7. Synthesis of the pigment [*(50a)*] from *P.lemonnieri* and of the homolog *(50b)*. (a), R = n-C_7H_{15}; (b), R = CH_3.

(50a). On hydrogenolysis and autoxidation, it is converted into diacetylindigoidine *(53b)*. All the intermediates of this reaction have been trapped, and the reaction course has been shown to be similar to that indicated in Scheme 3.

4. Biogenesis of the Azaquinones

Though aminocitrazinic acid *(17)* and particularly aminoglutaconimide *(21)* readily form indigoidine *(3)* on autoxidation[20], it was not possible to detect the obvious biosynthesis path, in which glutamine is cyclized to aminoglutarimide, which is then dehydrogenated to aminoglutaconimide. Neither intact nor ruptured cells of *Corynebacterium insidiosum* were able to transform aminoglutarimide or phthalimidoglutarimide (thalidomide) into indigoidin[30].

On the other hand, 2,6-pyridinediol appears to be the common precursor in a synthesis path leading both to indigoidine and to indochrome. Feeding with 2,6-pyridinediol considerably increases the yield of indigoidine in cultures of *C. insidiosum*[31]. 3-D-Ribosyl-2,6-pyridinediol (deazauridine) *(49)* has been isolated from cultures of the wild strain of *Arthrobacter polychromogenes*, and is immediately converted into indochrome by an indochrome-free mutant of *A.polychromogenes*[32]. A monooxygenase (synthesis of indigoidine) evidently competes with a ribosyl transferase (synthesis of indochrome) for the substrate 2,6-pyridinediol. Whereas both pigments are formed in a stationary culture, the monooxygenase reaction predominates in a strongly aerated shaking culture, so that indigoidine is almost exclusively formed. Indochrome formation occurs in the shaking culture only on addition of deazauridine *(49)*. Since this effect occurs immediately on addition of the substrate, the enzymes for the parallel pathway must already be present in indigoidine-producing cells. No bacterium that produces only indochrome has either been found in nature or produced by mutation. Mutation leads either to the loss only of the ability to form indochrome or to progeny that do not form pigments at

all. The indochrome-free mutant of *A. polychromogenes* thus differs from the wild strain only in the lack of a ribosyl transferase.

In the biosynthesis of indigoidine from 2,6-pyridinediol, 2,3,6-pyridinetriol should be the further reaction product. A corresponding reaction has recently been detected in the degradation of 2,6-pyridinediol by *Arthrobacter oxydans* by identification of 2,3,6-pyridinetriol as an intermediate[25] and isolation of the corresponding monooxygenase[33]. As in autoxidation, the pyridinetriol is converted into *(1)* ("nicotine blue I")[4]. A second readily soluble pigment ("nicotine blue II") is also formed, particularly in the early exponential growth phase. This latter compound is formed *in vitro* on autoxidation of 2,3,6-pyridinetriol in the presence of 2,6-pyridinediol[34, 4]. Its synthesis agrees with the structure derived from spectroscopic data.

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COMMUNICATIONS

Direct Proof of the Non-aromaticity of Phospholes and Arsoles[1]

By *Werner Schäfer, Armin Schweig, Gottfried Märkl, Hagen Hauptmann,* and *François Mathey*[*]

Physicochemical investigations (X-ray structure analysis[2e,g], UV[2a-d,o], NMR[2a-d,f,h-k,n], dipole moment[2l,4b], and reaction kinetic measurements[2m] as well as theoretical-chemical[3a-c] and chemical[2a-d,k,o,4a,b] studies of the participation of the lone pairs of hetero atoms in cyclic conjugation (aromaticity) in phospholes and arsoles have so far had contradictory results. We now describe a direct proof of the non-aromaticity of these systems.

Figure 1 shows the photoelectron spectra[5] of 1-phenylphosphole *(1)*, 1-phenylphospholane *(2)*, 2,5-dimethyl-1-phenylphosphole *(3)*, and 2,5-dimethyl-1-phenylarsole *(5)*, and Figure 2 displays the correlation diagram for the highest occupied MO's of *(1)* to *(5)* derived from these spectra and that of 2,5-dimethyl-1-phenylphospholane *(4)*. The spectrum of *(1)* shows two bands of relative intensity 1:1 in the region of lower ionization potentials (IP). From the position (9.25 eV; $e_{1g}(\pi)$ MO in benzene, 9.24 eV[5]) and the form of the second band (no splitting) it follows that there is no interaction between the phenyl substituent and the phosphole system of *(1)*[6]. The relative intensity of the first band indicates that there must be two ionizations in this region, these being assignable only to the antisymmetric MO ($a_2(\pi)$ in cyclopentadiene, 8.57 eV[7]) and the lone pair of the phosphorus atom [8.35 eV in *(2)*]. This

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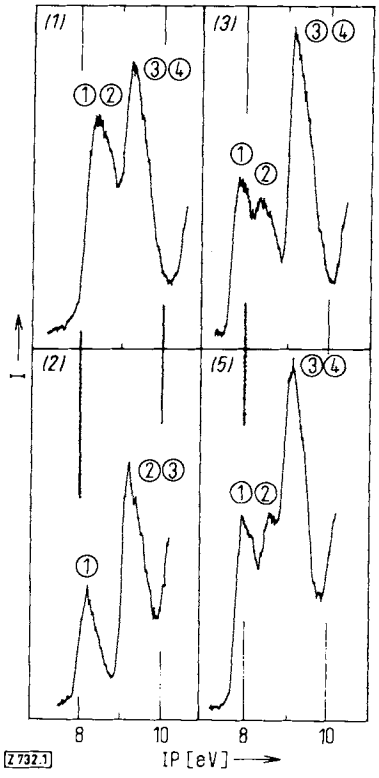

Fig. 1. PE spectra of the heterocycles *(1)*, *(2)*, *(3)*, and *(5)*.

assignment is wholly confirmed by comparison with the spectra of *(3)* and *(4)*. Methyl substitution in the 2,5-positions raises the π-MO to 8.0 eV[8] (as a result of the hyperconjugative coupling between the CH_3 groups and the π-MO), but the lone pair is influenced hardly at all. All the available arguments—the lone pair of PH_3 (10.59 eV)[10]

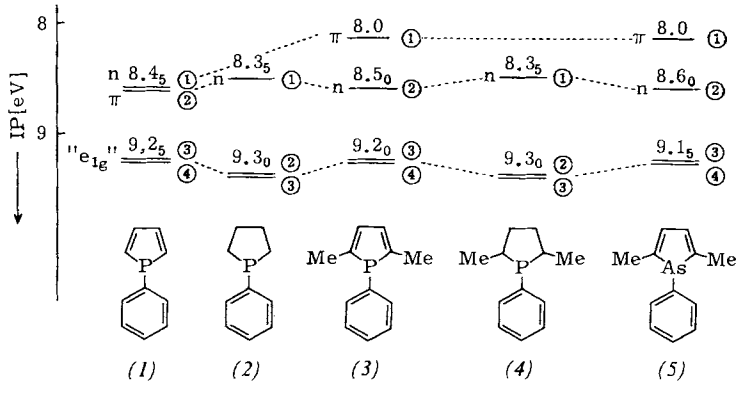

Fig. 2. Correlation diagram of the highest occupied molecular orbitals of compounds *(1)*—*(5)*.

and of AsH_3 (10.58 eV)[10] have equal energy, the π-HOMO (highest occupied MO) of *(3)* is almost a 1,4-dimethyl-*cis*-butadiene MO, and quantum-chemical approximations[3c]—make it probable that the same assignment is valid for *(5)* as for *(3)*.

Our results show that there is no conjugative interaction between the five- and the six-membered ring in any of the compounds studied [the e_{1g} (π) MO's of benzene are not split in *(1)* to *(5)* and retain almost constant energy]. Our results further show that the lone pairs in the phospholes *(1)* and *(3)*, and very probably also in the arsole *(5)*, take no part in a cyclic five-membered ring conjugation (saturation of the *cis*-butadiene system in the five-membered ring has no noticeable influence on the energy of the lone pair). Accordingly, phospholes and arsoles in their ground-state conformations consist of localized diene systems and lone pairs of hetero atom electrons. In this sense phospholes and arsoles are not aromatic.

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Preparative-Scale Synthesis of (1 *R*)- and (1 *S*)-Monodeuteriopropanol by Enzymatic Exchange Reactions

By *Helmut Günther*, *Florian Biller*, *Max Kellner*, and *Helmut Simon*[*]

The optical activity of chiral compounds of the type $CRR'H^2H$ and the stereochemistry of their reactions are of considerable interest[1-4]. Chemical methods for their preparation seldom lead to high stereochemical purity[3,4]. Enzymatic reactions on a preparative scale are usually very demanding[5]. An enzyme-catalyzed exchange reaction involving no isolation of intermediates is appreciably simpler and generally applicable for preparation of (*R*)- and

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(*S*)-enantiomers of numerous compounds[6]. Thus a diaphorase brings about exchange between the hydrogen atoms of the pyridine nucleotide coenzyme and those of water. Owing to the reversibility of the NAD-dependent dehydrogenase reactions this leads also to stereospecific exchange between the hydrogen atoms of the substrate and those of the medium.

In the present communication we describe the preparation of the hitherto unrecorded (1*R*)-[1-^{2}H]- and (1*S*)-[1-^{2}H]-propanols[7]. It seems that this is also the first time that both enantiomers of a compound that is chiral because of substitution by deuterium have been synthesized on a preparative scale.

Experimental:

In all the compounds named below the labile-bound protium was replaced by deuterium atoms before the incubation.

The following were incubated together in D_2O (290 ml) at 35 °C: phosphate buffer (pD = 8.0) 22.4 mmol, ethylenediaminetetraacetic acid 100 mg as sodium salt, albumin (recrystallized five times) 200 mg from hens' egg white, NAD^+ 50 mg, NADH 50 mg, diaphorase 5200 U[**], yeast alcohol dehydrogenase 22500 U[***], and 1-propanol 10.5 ml. The exchange of *pro-R*-protium of the propanol was determined in an aliquot portion after 25 h and again after 42 h by NMR spectroscopy and was found to be 97 ± 5%. The propanol was extracted with dry, ethanol-free ether; the solution was concentrated, whereafter 7.0 ml propanol containing 13.5 vol.-% of water were obtained by preparative gas chromatography. The 3,5-dinitrobenzoate of this propanol showed 0.97 ± 0.01 atom of deuterium per molecule on mass spectroscopy[8].

10.5 ml of [1,1-$^2H_2$]propanol were incubated analogously in H_2O for 45 h and then worked up. The water content of the product was 17.4% and the 3,5-dinitrobenzoate contained 1.29 ± 0.01 atoms of deuterium per molecule; the exchange in this case amounted to only 71.3%.

Table 1. Specific rotations [a] of the monodeuteriopropanols, calculated for anhydrous material with a ^{2}H-content of 1.0 atom per molecule.

λ [nm]	(1*R*)-[1-^{2}H]-Propanol $[\alpha]_D^{20}$ [°]	(1*S*)-[1-^{2}H]-Propanol $[\alpha]_D^{20}$ [°]
220	—	7.36 [b]
240	−5.17	5.29 [b]
257	−4.12	4.19
302	−2.65	2.70
365	−1.58	1.64
400	−1.24	1.29
500	−0.72	0.75
589	−0.50	0.51

[a] Measurements were made with a Jasco-Spectral polarimeter J 5. Unless otherwise stated, the samples contained 15 vol.-% of water.

[b] Values determined on 3.5% aqueous solutions.

Table 1 shows the specific rotations for various wavelengths. The agreement between the absolute values shows that there is no optically active impurity in the preparations, since it is extremely unlikely that these would have different signs in the two enantiomers.

The molar rotations of (1*R*)-[1-^{2}H]ethanol and of the corresponding propanol and butanol are $[M]_D = 0.14°$[5,9], −0.29°, and −0.35°[10], respectively. The difference between $[M]_D$ for ethanol and propanol is 0.43° but for propanol and butanol only 0.06° which is not with certainty significant.

Brewster[1] predicted that (1*R*)-[1-^{2}H]butanol would be *ca.* 0.33° more levorotatory than ethanol.

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Boron Tris(trifluoroacetate) for Removal of Protecting Groups in Peptide Chemistry

By *J. Pless* and *W. Bauer*[*]

Boron compounds have been used for removal of protecting groups only on rare occasions[1-4].

We have found that, in CH_2Cl_2, BBr_3 and BI_3, but not BF_3 or BCl_3, effect quantitative removal, under very mild conditions, of the benzyloxycarbonyl (Z) group that is very frequently used in peptide chemistry, and do not thereby attack OH groups of serine or threonine or SH groups of cysteine. Ester groups are, however, partially hydrolyzed to acid, and a further disadvantage is the use of CH_2Cl_2 which is not a good solvent for the longer peptides.

When trifluoroacetic acid is used as solvent instead of CH_2Cl_2, BBr_3 forms boron tris(trifluoroacetate) (BTFA)[5]:

$$3CF_3COOH + BBr_3 \rightarrow B(OOCCF_3)_3 + 3HBr$$

For the cleavage experiments this reagent (BTFA) can be easily isolated (see Experimental) and can be used in CH_2Cl_2 or preferably in trifluoroacetic acid. BTFA removes Z and other acid-labile groups as smoothly as BBr_3, but does not cause hydrolysis of esters or other side reactions. Surprisingly, BTFA is also suitable for smooth removal of other side-chain protecting groups used for arginine and cysteine (see Table 1) that have hitherto required drastic conditions[6,7].

Experimental:

Equivalent amounts of BBr_3 and CF_3COOH are mixed at 0 °C in CH_2Cl_2, whereupon a precipitate is formed. The

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Table 1. Protecting groups that are removable or not removable by BTFA.

Removable protecting groups	
Amino-protecting groups:	Z, Boc, Nps, Trt, or other acid-labile protecting groups
Carboxyl-protecting groups:	benzyl (also polymer bound)
Side-chain-protecting groups:	Arg(NO_2), Arg(Tos), Cys(*p*-MeO-Bzl), Ser(Bzl), Thr(Bzl), Tyr(Bzl)
Non-removable groups	
COOMe, COOEt, R—OMe (ether), —CONH—	

mixture is evaporated to dryness at 20 °C in a vacuum. The residue is dissolved in CF_3COOH and this solution is used directly for the group cleavage. For this purpose the protected compound is dissolved in CF_3COOH and treated with at least 3 equivalents of BTFA in CF_3COOH at 0 °C. For removal of nitro, tosyl or *p*-methoxybenzyl groups, 5—8 equivalents of BTFA are needed. An even greater excess of reagent becomes necessary with increasing chain length of the peptide. After 1 h the solution is evaporated at room temperature and the residue is worked up. The boron compounds can be removed by repeated evaporation with methanol or by chromatography.

The new reagent thus has a similar action to liquid HF but does not require special cautionary measures or apparatus. Biologically active peptides have already been successfully prepared using this technique.

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sp^2-Hybridization on the Sulfur-substituted Nitrogen in Diethyl 2,2-(Heptasulfane-1,7-diyl)-1,1-hydrazinedicarboxylate[1]

By *Karl-Heinz Linke, Dietmar Skupin, Johann Lex*, and *Bernward Engelen*[*]

By treating diethyl 1,1-hydrazinedicarboxylate with dichlorodisulfane or dichloroheptasulfane we recently synthesized a hydrazine that was substituted on the same nitrogen atom by two sulfur atoms, namely diethyl 2,2-(heptasulfane-1,7-diyl)-1,1-hydrazinedicarboxylate *(1)*[2]. For the study of bonding in hydrazines having substituents with free d-levels it seemed important to us to have an X-ray structure analysis of *(1)*, in particular to establish the (p→d)π contribution to the N—S bonds.

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Compound *(1)* crystallizes in the monoclinic form with lattice constants $a = 8.85_7$, $b = 31.99_2$, $c = 11.61_5$ Å, $\beta = 98.7°$. The density determined by the flotation method amounts to 1.60 g cm^{-3}, corresponding to 8 molecules per unit cell ($d_{calc.} = 1.625$ g cm^{-3}). The systematically absent reflections and the symmetry of the reflection intensities lead to the space group $P2_1/n$. For the three-dimensional X-ray structure analysis the intensities of 2288 independent reflections were determined photographically by the multi-film method from precession exposures. The structure was calculated by the direct method with the program system X-RAY 70[3] on IBM computers 360/75 and 370/165 in the Zentralinstitut für Angewandte Mathematik der Kernforschungsanlage in Jülich. The isotropic refinement by the method of least squares for the nitrogen, sulfur and carbon atoms provided an *R* value of 0.157; hydrogen atoms were not considered.

The asymmetric unit contains two molecules of *(1)*. The bond lengths, bond angles, and dihedral angles of these two molecules, determined independently of one another, show significant differences in the region of the hydrazine group. The bond lengths and bond angles of molecule I can be seen in the schematic representation of *(1)* in Fig. 1. The relatively high standard deviations (see legend) are to be ascribed to the limited accuracy with which the intensities can be determined from films and to the large number of atom parameters to be determined for each molecule.

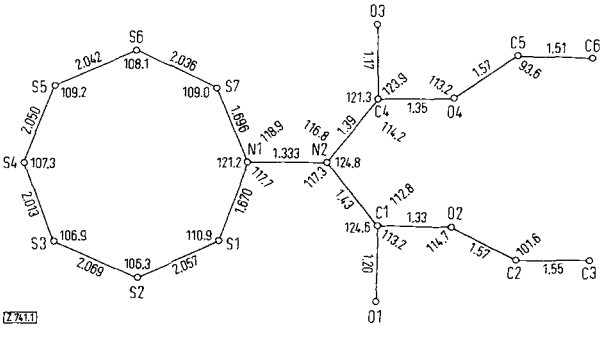

Fig. 1. Bond lengths (Å) and bond angles (°) in diethyl 2,2-(heptasulfane-1,7-diyl)-1,1-hydrazinedicarboxylate (molecule I). Standard deviation of bond lengths and angles: σ_{S-S} 0.009—0.012 Å; σ_{S-N} 0.020—0.022 Å; σ_{N-N} 0.028 Å; σ_{N-C} 0.03 Å; σ_{C-O} 0.03—0.04 Å, σ_{C-C} 0.04—0.06 Å; σ_{S-S-S} 0.5°; σ_{S-S-N} 0.8—0.9°; σ_{S-N-S} 1.3°; σ_{S-N-N} 1.5—1.6°; σ_{N-N-C} 1.8—2.2°; σ_{N-C-O} 1.9—2.3°; σ_{O-C-O} 2.3—2.5°; σ_{C-O-C} 1.9—2.8°; σ_{O-C-C} 2.1—3.3°.

The sulfur-nitrogen ring of *(1)* exists in the crown form, with the ester groups in a plane almost perpendicular to this ring. The nitrogen atom forming part of the ring in molecule I shows complete sp^2 hybridization which can be explained by formation of dative π-bonds from the nitrogen to the sulfur atoms. The angle between the planes defined by the atoms S1-N1-S7 and S1-N1-N2 is found to be 179.9°, so that a planar arrangement of the atoms around the ring-nitrogen atom N1 is proved. In agreement with this are the N—N distance and the two N—S bond lengths which are significantly shorter than the known values for corresponding single bonds, namely, *ca.* 1.45 and 2.76 Å, respectively.

In molecule II there are also strong double-bond contributions between the ring-nitrogen atom and the sulfur atoms to be observed, but sp^2 hybridization of the nitrogen is incomplete. The angles S1-N1-S7, N2-N1-S1, and N2-N1-S7 in molecule II were determined as 121.1 ($\sigma = 1.3$), 118.6

($\sigma = 1.5$) and 115.5° ($\sigma = 1.7°$), respectively; the angle S1-N1-S7/S1-N1-N2 here amounts to 154.7°. The two N—S distances are 1.64 and 1.70 Å severally, and the N—N bond length is 1.42 Å.

No simple explanation can be given for the difference between the observed N—S and N—N bond lengths in molecules I and II. Calculation of the contact separations does not show any marked intermolecular interaction, so that these differences may be due to lattice forces that perhaps lead to more favorable total positioning of the two relatively large and bulky molecules in the unit cell. Severe hindrances can be observed in the neighborhood of the hydrazine group, and these may be responsible for the poor yield of *(1)* and the difficulty in crystallizing the compound.

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[1] Part 37 of the Chemistry of Hydrazine and its Derivatives. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.—Part 36: *K.-H. Linke, R. Taubert*, and *Th. Kruck*, Z. Anorg. Allg. Chem., in the press.

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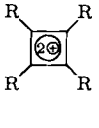
[3] We thank the Abteilung für Röntgenstrukturforschung of the Max-Planck-Institut für Eiweiss- und Lederforschung in München for supplying a modified version of the program X-RAY 70.

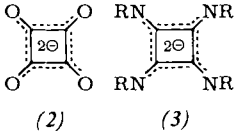
Alkylation and Redox Behavior of a Squaric Amidine[**]

By *Siegfried Hünig* and *Hermann Pütter*[*]

Cyclobutene dications *(1a)* and *(1b)* can be conclusively shown to exist as 2π Hückel aromatic compounds in strongly acidic media at low temperature[1-3], but they cannot be isolated. It would be expected that the donor action of four amino groups, as in *(1d)*, would make it possible to isolate the dication. The effect of hydroxyl groups[3] is insufficient for this.



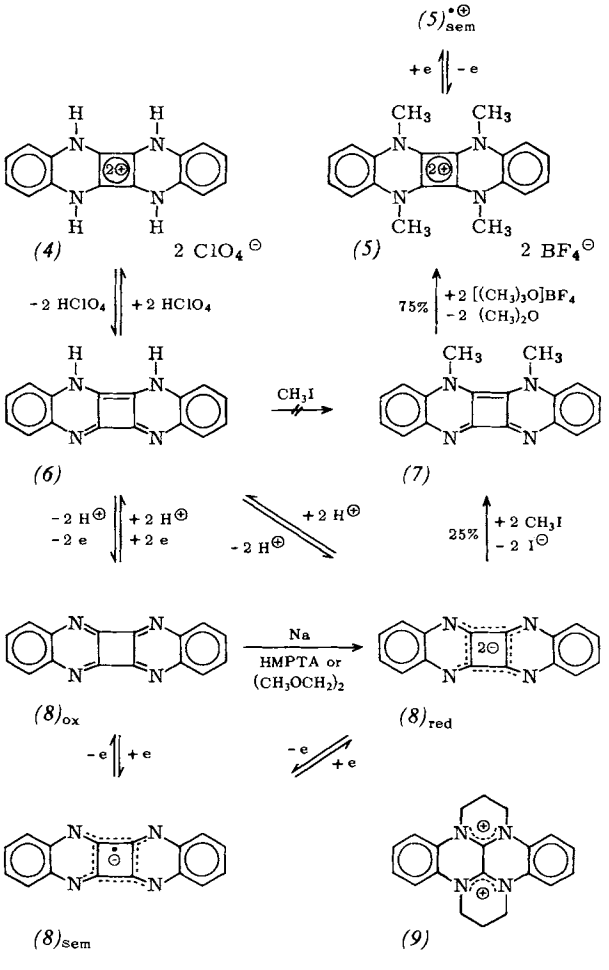
(1a), R = CH_3
(1b), R = C_6H_5
(1c), R = OH
(1d), R = NR^1R^2



(2) *(3)*

The salt *(4)* was recently described[4] and is the first representative of type *(1d)*, but because of its sparing solubility the proton distribution remained unproved.

We have now succeeded[5] in synthesizing the green tetramethyl derivative *(5)*, m.p. 262 °C (dec.)[6], whose structure follows unambiguously from the NMR spectrum [$\delta(CF_3COOH) = 3.2$ (s/12H), 6.5—7.1 ppm (m/8H)]. *(5)* is thus to be considered a salt with a stable cyclobutenium dication of type *(1d)*. Its electron spectrum is almost superposable on that of *(4)*, so that the structure of the latter is also ensured[7]. Analogously to the dication *(9)*[8] of related structure, the salt *(5)* takes up one electron at −0.67 V[9]; however, unlike *(9)*, it cannot be further reduced until −1.6 V, *i.e.* with an additional expenditure of energy amounting to 20 kcal/mol, which is a further indication of the antiaromatic destabilization energy[10] in the cyclobutadiene derivative that would result.



The synthesis of *(5)* from $(8)_{red}$ is effected by way of *(7)*, a suspension of which in ethylene dichloride is alkylated by trimethyloxonium tetrafluoroborate (4h under reflux). Although *(4)* undergoes ready reversible deprotonation to the bisamidine *(6)*[4], it cannot be methylated to yield *(7)*, even in the presence of an auxiliary base. *(7)* is formed, however, from the dianion $(8)_{red}$ by methyl iodide[11]. $(8)_{red}$ is reversibly oxidizable in two steps to $(8)_{ox}$[4], the reaction proceeding *via* the thermodynamically unusually stable $(8)_{sem}$ ($K_{sem} = 2 \times 10^{15}$!) [$(8)_{red} \rightarrow (8)_{sem}$, $E_2 = -1.47$ V, in DMF; $(8)_{sem} \rightarrow (8)_{ox}$, $E_1 = -0.57$ V, in DMF]. $(8)_{sem}$, formed as a brownish-red solution of $(6) + (8)_{ox}$ in DMF/K *tert*-butoxide[12], shows a fully resolved ESR spectrum, in which not only all the N atoms, but also all the H atoms, possess the same coupling constants (Fig. 1).

The squaric acid dianion *(2)* has been described as a typical example of the series $C_nO_n^{2\ominus}$, the aromatic "oxocarbons"[13], which are oxidizable. With nitrogen as substituent the series $C_n(NR)_n^{2\ominus}$, the aromatic "iminocarbons"[14], is to be expected[15], and $(8)_{red}$ is the first example thereof.

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[**] These investigations were supported by the Fonds der Chemischen Industrie, Dechema and the Badische Anilin- & Soda-Fabrik AG.

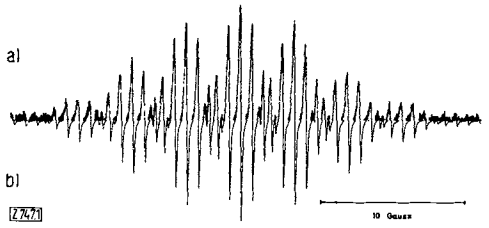

Fig. 1. a) ESR spectrum of $(8)_{sem}$ in DMF/K *tert*-butoxide. b) Simulated spectrum with $a_H = 0.80$ and $a_N = 3.75$.

The radical ion $C_4O_4^{\ominus}$ has been merely postulated[13] as formed on oxidation of *(2)*, and cyclobutanetetraone is known only as tetrahydrate[13]. However, all three oxidation states have been proved to exist for the iminocarbons *(8)* of type $C_4(NR)_4$ *(3)* described in this communication.

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[1] *G. A. Olah, J. M. Bollinger,* and *A. M. White,* J. Amer. Chem. Soc. *91*, 3667 (1969).

[2] *G. A. Olah* and *G. D. Mateescu,* J. Amer. Chem. Soc. *92*, 1430 (1970); *G. A. Olah, A. M. White,* and *D. H. O'Brien,* Chem. Rev. *1970*, 1950.

[3] *G. A. Olah* and *A. M. White,* J. Amer. Chem. Soc. *89*, 4752 (1967).

[4] *S. Hünig* and *H. Pütter,* Angew. Chem. *84*, 481 (1972); Angew. Chem. internat. Edit. *11*, 431 (1972).

[5] From the Dissertation by *H. Pütter,* Universität Würzburg 1972.

[6] Elemental analyses accord with the required values.

[7] λ_{max} [nm] (ε) in HCOOH: *(4)*: 629 (1300), 580 (1150), 412 (24400), 392 (28600), 342 (32000), 282 (29500), 273 (26400); *(5)*: 644 (1930), 596 (1610), 425 (30300), 407 (33200), 343 (28900), 283 (32100), 274 (26200).

[8] *S. Hünig, D. Scheutzow,* and *H. Schlaf,* Liebigs Ann. Chem., in press.

[9] Polarography in benzonitrile with $(C_2H_5)_4N^{\oplus}BF_4^{\ominus}$ as supporting electrolyte, Hg or Pt electrode against Ag/AgCl in acetonitrile.

[10] *R. Breslow,* Pure Appl. Chem. *28*, 3 (1971).

[11] Presumably also two methyl groups enter just one quinoxaline ring, so that an unstable cyclobutadiene derivative results [cf. *(7)* in Ref. [4]].

[12] It is not yet certain whether the ESR signal of the violet-brown solutions of *(5)* in DMF or formic acid/zinc arises from the species $(5)_{sem}$.

[13] *R. West* and *J. Niu* in *T. P. Snyder:* Nonbenzenoid Aromatics. Academic Press, New York 1969.

[14] Steric effects of R can lead to limitations.

[15] The same is true for mixed "oxo-iminocarbons" (cf. Ref. [5]).

A New Mechanistic Concept for the Bicyclopropenyl Rearrangement[1]

By *Robert Weiss* and *Steffen Andrae*[*]

The often cited[2, 3] study by *Breslow et al.*[4] (Scheme 1) is the only work hitherto reported on the course of thermal isomerization of the bicyclopropenyl derivative *(1)* to the benzene derivatives *(5)* and *(6)*.

Doubt is, however, thrown on the formation and/or nature of the hypothetical intermediates *(2)*—*(4)* for the following reasons:

1. The reaction *(1)*→*(2)* is forbidden by the Woodward-Hoffmann rules and also leads to an increase in strain energy.

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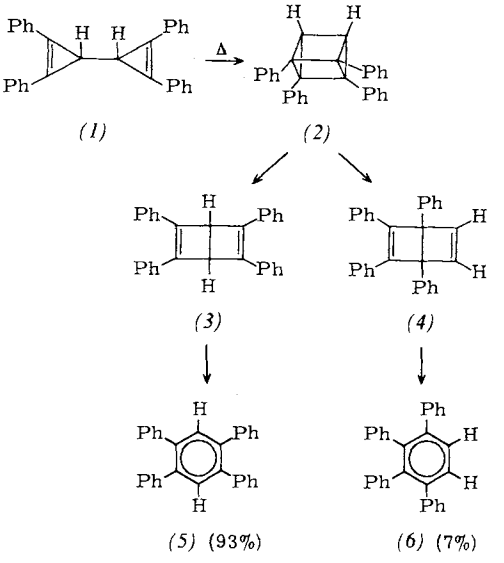
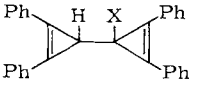


Scheme 1

2. From experience in prismane chemistry[2d] it would be expected that thermal isomerization of *(2)* should produce a benzvalene intermediate which, *inter alia*, should cause formation of the *meta*-isomer of *(5)* and *(6)*.

These objections, and our observation that *(3)* can be obtained from *(1)* by $Ag^{\oplus}$ catalysis[1], induced us to undertake a more detailed study of the bicyclopropenyl rearrangement including its $Ag^{\oplus}$ catalysis.



(7a), X = CH_3 [5]
(7b), X = OCH_3 [5,6]
(7c), X = CN [5,6]

According to NMR analysis the action of an equimolar amount of $AgClO_4$ on the model substance *(7a)* in anhydrous C_6H_6 at 50°C is complete in 2 h and gives exclusively *(8)* and *(9)*.

(9) (CH_3 signal at τ = 7.79) could be obtained pure from the reaction mixture by recrystallization and was identified by comparison with an authentic specimen[7].

The structure of *(8)*, which was not obtained completely free from entrained *(9)*, was proved by the following data:

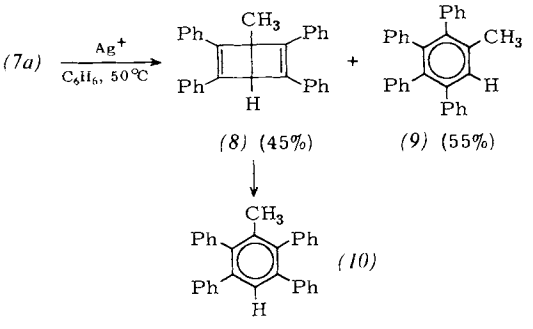
1. The UV spectrum ($CHCl_3$) exhibited $\lambda_{max} = 295$ nm with log ε = 4.33 which is characteristic of two substantially independent *cis*-stilbene chromophores[1].

2. In the NMR spectrum, *(8)* shows, besides aromatic protons, a CH_3 signal at τ = 8.22 (s) and the signal of one methine proton at τ = 5.93 (s). In particular the position of the last signal is characteristic of a Dewar-benzene of this structural type[1].

3. Finally, *(8)* was aromatized in boiling toluene with a half-reaction time of 3 h to 1-methyl-2,3,5,6-tetraphenylbenzene *(10)* [identical with an independently synthesized sample[8]: m.p. 269—270°C, NMR ($CDCl_3$): τ = 8.04 (3H/s), 2.83 (10H/s), 2.81 (10H/s), 2.26 (1H/s)].

Thermal rearrangement of *(7a)* in boiling $(CH_2Cl)_2$ (to avoid acid catalysis this solvent was previously chromatographed over basic Al_2O_3) afforded after 4 weeks the benzene derivatives *(9)* (30%) and *(10)* (70%) as sole end-products. In this reaction it is remarkable that the Dewar-benzene derivative can be shown unambiguously by NMR

spectroscopy to be an intermediate in the formation of *(10)* [composition of the reaction mixture after 331 h: *(7a)* 57%, *(8)* 9%, *(9)* 13%, *(10)* 21%]. This is the first successful[3] direct proof of a Dewar-benzene intermediate in the thermal rearrangement of a bicyclopropenyl which is due to the high stability of *(8)* [compared with that of *(3)*[1]].



Furthermore, the products and product distribution (Table 1) show that thermal and Ag^I-catalyzed rearrangements are closely related processes both in the case of *(1)* and in that of *(7a)*. In particular, the fact that for *(1)* the product composition is almost identical in the two types of rearrangement (cf. Table 1) shows that in this case the conversion of a sequence of symmetry-forbidden processes (Scheme 1) into a sequence of symmetry-allowed processes can hardly be a function of Ag^I[10]. Scheme 1 is also unable to explain the great influence of the bridgehead substituent in *(7a)* on the product distribution that results from thermal rearrangement.

Table 1. Results of thermal and Ag^I-catalyzed rearrangement of *(1)* and *(7a)* [9].

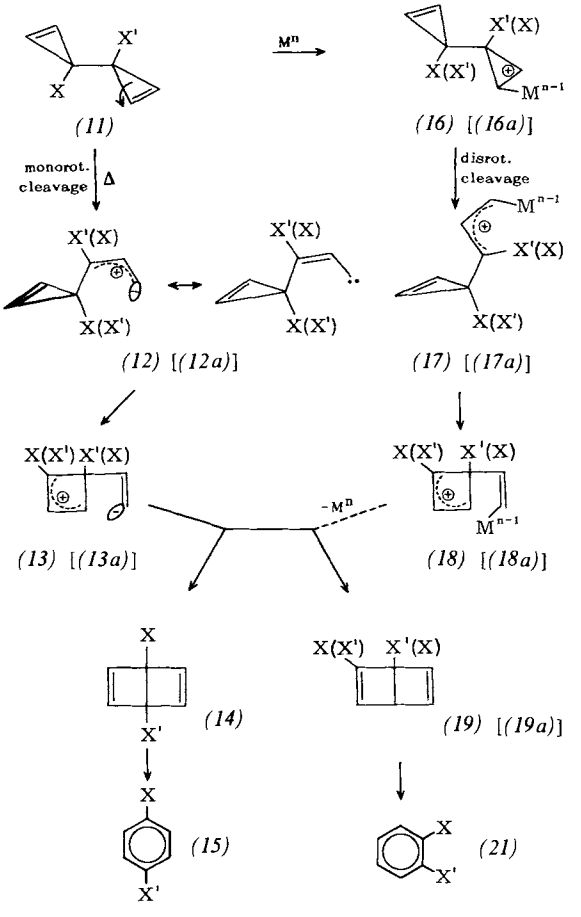
Cpd.	Rearrangement	*o*-Series [a]	*p*-Series [a]
(1)	Δ	7% *(6)* [4]	93% *(5)* [4]
(1)	Ag^I	5% *(6)* [b]	95% *(5)* [b]
(7a)	Δ	30% *(9)*	70% *(10)*
(7a)	Ag^I	55% *(9)*	45% *(10)*

[a] This assignment refers to the position of the bicyclopropenyl bridgehead substituents in the rearrangement products (benzene or Dewar-benzene).

[b] As we have now found, *(6)* is also formed to a small extent as product of the Ag^I-catalyzed rearrangement of *(1)* [1]; *St. Andrae*, Diplomarbeit, Universität München, 1972.

However, an adequate interpretation of all the experimental material on the bicyclopropenyl rearrangement can be based on the new mechanistic concept formulated in Scheme 2.

The *thermal* bicyclopropenyl rearrangement of *(11)* is, according to Scheme 2, initiated by a reversal of the formation of a cyclopropene[11], namely a retrocarbene fission[12] to afford the singlet carbene[13] *(12)* [*(12a)*]. Then follows the reaction *(12)* [*(12a)*]→*(13)* [*(13a)*] which is a ring expansion of the known cyclopropenylmethyl cation→cyclobutenyl cation type[14] that occurs with extreme ease. If the monorotatory[15] opening of the cyclopropene ring of *(11)* occurs from the transoid conformation, it leads directly to the bisected conformation of the vinylcarbene *(12)* [*(12a)*] required for the ring expansion (cf. Scheme 2). This would provide a good possibility that the ring opening and ring expansion sequence could be coupled in an energetically favorable manner, *i.e.* could occur as a concerted process (in which case *(12)* [*(12a)*] would not be a true intermediate in the bicyclopropenyl rearrangement). These reactions would be followed by final reaction of the inner ion pair *(13)* [*(13a)*] to give the isomeric Dewar-benzenes *(14)* and *(19)* [*(19a)*] in the product-determining step (see below) with, under some conditions, their aromatization.



Scheme 2

The most likely *function of* Ag^I in the rearrangement is catalysis of the retrocarbene fission (retrocarbene cleavage of cyclopropenes by Cu^I[16] and Tl^{III}[17], for instance, is known). This could consist in the (sterically favorable) *exo*-attack by Ag^I on *(11)* and rapid disrotatory opening of *(16)* [*(16a)*] to give *(17)* [*(17a)*]. With the ring expansion to *(18)* [*(18a)*] the reaction follows the same path as in the thermal case and should proceed to exactly the same result.

Application of Scheme 2 to *(1)* [*(11)*, X=X'=H] shows that in its thermolysis retrocarbene cleavage must be the rate-determining step; if its activation energy is lowered by Ag^I-catalysis then the Dewar-benzene derivative *(3)* becomes isolable. In neither type of rearrangement can the Dewar-benzene derivative corresponding to *(19)* [*(19a)*] be detected—its structure differs in type from that of *(4)* (cf. Scheme 1); presumably conversion into *(6)* is greatly facilitated by the phenyl group on the bridgehead[18]. Finally the *o*/*p*-product ratio in the thermolysis reflects the competitive situation of the cyclobutenyl cation in *(13)* [*(13a)*] (X=X'=H) *vis à vis* the vinyl anion: there nucleophilic addition to the more electrophilic 1-position with conservation of conjugation between the phenyl groups

would be expected to preponderate very largely[19], which accords with the experiment (see above). According to Scheme 2 the same situation should occur on Ag^I-catalysis since there *(13)* [*(13a)*] is again postulated as intermediate: the almost identical *o/p*-ratio (see Table 1) is visible confirmation thereof.

The influence of the bridgehead substituent in *(7a)* on the product distribution can be understood in view of the intermediate *(13)* ($X=CH_3$, $X'=H$): the CH_3 group, which stabilizes carbenium ions, acting on position 1 increases the amount of ring closure at position 3 and thus also increases formation of the representative of the *o*-series. On Ag^I-catalysis, however, this intermediate should have a statistically greater effect than in the thermolysis, because for steric reasons attack by Ag^I should be favored on the cyclopropene ring with the unsubstituted bridgehead, whereas thermal retrocarbene cleavage should occur preferentially by way of *(12)* ($X=H, X'=CH_3$; carbenium ion stabilization!). On this basis the different *o/p*-ratios formed by the two routes become intelligible (cf. Table 1).

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[1] Reactions of Coupled Three-Membered Rings, Part 2. Part 1 is considered to be the paper by *R. Weiss* and *C. Schlierf*, Angew. Chem. *83*, 887 (1971); Angew. Chem. internat. Edit. *10*, 811 (1971). This work was supported by the Deutsche Forschungsgemeinschaft.

[2] a) *R. Breslow* in *P. De Mayo*: Molecular Rearrangements. Interscience, New York 1963, Vol. I, p. 244; b) *G. L. Closs*, Advan. Alicycl. Chem. *1*, 90 (1966); c) Houben-Weyl: Methoden der Organischen Chemie. Thieme, Stuttgart 1971, Vol. 4/3, p. 720; d) *L. T. Scott* and *M. Jones jr.*, Chem. Rev. *72*, 181 (1972).

[3] *E. E. van Tamelen, S. P. Pappas*, and *K. L. Kirk*, J. Amer. Chem. Soc. *93*, 6092 (1972).

[4] *R. Breslow, P. Gal, H. W. Chang*, and *L. J. Altmann*, J. Amer. Chem. Soc. *87*, 5139 (1965).

[5] Preparation: *R. Weiss, St. Andrae*, and *C. Schlierf*, unpublished work.

[6] *R. Weiss* and *St. Andrae*, Angew. Chem. *85*, 147 (1973); Angew. Chem. internat. Edit. *12*, 152 (1973).

[7] *D. Seyferth, C. Sarafidis*, and *A. B. Evnin*, J. Organometal. Chem. *2*, 417 (1964).

[8] *R. Weiss* and *M. Seitz*, unpublished work.

[9] No noticeable solvent-dependence was observed for the product distributions.

[10] *R. Pettit, H. Sugahara, J. Wristers*, and *W. Merk*, Discuss. Faraday Soc. *47*, 71 (1969).

[11] *G. L. Closs, L. E. Closs*, and *W. A. Böll*, J. Amer. Chem. Soc. *85*, 3796 (1963).

[12] Reversible thermal retrocarbene cleavage of a cyclopropene was very recently demonstrated for the first time: *E. J. York, W. Dittmar, J. R. Stevenson*, and *R. G. Bergman*, J. Amer. Chem. Soc. *94*, 2882 (1972).

[13] Formulation of the vinylcarbene *(12)* [*(12a)*] in the singlet form appears particularly justified in the cases *(1)* and *(7a)* closely studied by us (cf. also Ref. [6]) because there, apart from X and X', the phenyl and cyclopropenyl group are two donor groups that will stabilize the allyl cation portion of *(12)* [*(12a)*] and thus also the singlet form.

[14] *R. Breslow, J. Lockhart*, and *A. Small*, J. Amer. Chem. Soc. *84*, 2793 (1962).

[15] This process consists of (heterolytic) cleavage of one cyclopropene bond with simultaneous rotation around the other.

[16] *H. H. Stechl*, Chem. Ber. *97*, 2681 (1964).

[17] *T. Shirafuji, Y. Yamamoto*, and *H. Nozaki*, Tetrahedron Lett. *1971*, 4713.

[18] In work analogous to our previous investigation [1], *W. H. de Wolf, J. W. van Straten*, and *F. Bickelhaupt* (Tetrahedron Lett. *1972*, 3509) also found a Dewar-benzene of the type *(19)* [*(19a)*] postulated by us, but without explaining its occurrence. Thus the correctness of our views about this point in the topology of the bicyclopropenyl rearrangement is completely proven.

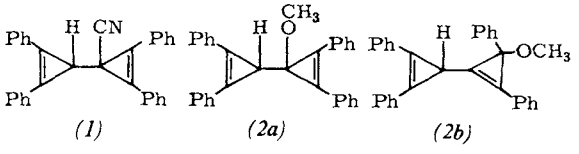
[19] The electronically very similar 2,3-diphenylcyclopropenylium ion shows a quite analogous behavior towards nucleophiles: *R. Breslow, J. Lockhart*, and *H. W. Chang*, J. Amer. Chem. Soc. *83*, 2375 (1961).

Formation of a Dewar-Anisole by Bicyclopropenyl Rearrangement

By *Robert Weiss* and *Steffen Andrae*[*]

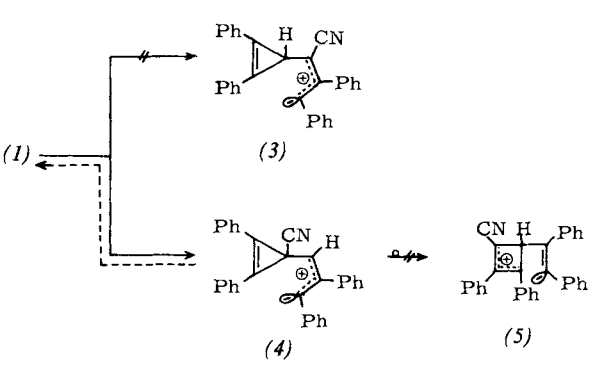
According to our mechanistic concept[1] it should be possible to influence the course of rearrangement of bicyclopropenyl systems to benzene derivatives in specific manners by means of bridgehead substituents; in particular, donor substituents should make rearrangement easier and acceptor substituents should hinder it. Because of their similar mechanisms we should expect also a general parallelism between the effects on thermal and on Ag^I-catalyzed rearrangements[1].

We have tested these hypotheses on the model substances *(1)* [1] and *(2a)/(2b)*[1,2].



(1) *(2a)* *(2b)*

The cyano compound *(1)* proved to be completely stable for days even in presence of a two-fold excess of Ag^I ions[3] in boiling anhydrous benzene. Thermally, *(1)* is stable for weeks up to 110°C in solution (at appreciably higher temperatures the substance decomposes without definite products being detectable). The lack of any tendency of *(1)* to aromatize is in striking contrast to the behavior of all previously known bicyclopropenyl derivatives[1] and, in particular, is incomprehensible on the basis of the mechanism proposed by *Breslow et al.*[1,4] for the bicyclopropenyl rearrangement. Our alternative mechanism, however, offers a simple explanation for the behavior of *(1)* (see Scheme 1): the retrocarbene fission *(1)*→*(3)* required for the thermal rearrangement of *(1)* (cf. Ref.[1]) is blocked by the CN group (α-cyano carbenium ion!). It is true that a (reversible) retrocarbene fission of the other cyclopropene ring, to give *(4)*, is possible (this point was not followed up) but then the CN group should prevent the ring expansion *(4)*→*(5)* (cf. Ref.[1]). Completely



Scheme 1

analogous arguments apply to the Ag^I-catalyzed rearrangement. In this way, one CN group on the bridgehead suffices to stabilize the whole bicyclopropenyl system.

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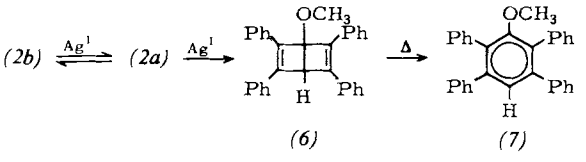
The ether *(2a)* supplies what in our mechanism is the electronic counterpart of *(1)*. Although investigation of the thermal rearrangement of *(2a)* had to be abandoned owing to tenacious contamination by *(2b)*[2], this difficulty could be overcome by Ag^I-catalysis. The action of an equivalent amount of Ag^I ions on a solution of a mixture of *(2a)* and *(2b)* in anhydrous benzene proceeded under uniquely mild conditions (5 min at room temperature) and almost exclusively[5] according to Scheme 2.



(6) (7)

Scheme 2

If the reaction was stopped after 5 min by extracting the Ag^I ions into H_2O, two new substances *(6)* (*ca.* 70%) and *(7)* (*ca.* 30%)[5] were detected by NMR spectroscopy in place of *(2a)*/*(2b)*.

The structure of *(6)* follows from the following data: 1. NMR spectrum: $\tau = 6.60$ (3H/s); 5.43[6] (1H/s); 2. UV spectrum: λ_{max} ($CHCl_3$) = 290 nm (log $\varepsilon \approx 4.40$)[1]; 3. Quantitative isomerization with a half-reaction time of *ca.* 20 min at 50 °C, to give *(7)*[7] which was identical with an authentic specimen[8].

(7) could be isolated as the sole final rearrangement product and was formed, according to Scheme 2, in at least 95% yield[5].

The observed course of the reaction can be interpreted in the sense that a mobile equilibrium between *(2a)* and *(2b)* is set up under the catalytic influence of Ag^I (corresponding to a reversible ether cleavage) and that *(2a)* is then removed by its Ag^I-catalyzed rearrangement to *(6)*. The fact that almost exclusively a representative of the *p*-series is thus formed[1] accords with our mechanistic model of the bicyclopropenyl rearrangement. According to that (cf. Ref.[1]) under the conditions used, only the cyclopropene ring substituted by the donor group in *(2a)* should be opened on electrophilic attack by Ag^I. In contrast to the case with a CH_3 group[1], steric hindrance of this *exo*-attack[1] is not to be expected for the OCH_3 group because of its conformational mobility, and this situation should result in almost exclusive formation of *(6)* (see Ref.[1]).

Compound *(6)* is the first example of a Dewar-benzene with a donor substituent on the bridgehead. Its extremely facile aromatization is of interest in connection with the nature of orbital-symmetry forbidden processes[9, 10]. The kinetic data are at present being determined.

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[1] Reactions of Coupled Three-Membered Rings, Part 3.—Part 2: *R. Weiss* and *St. Andrae*, Angew. Chem. *85*, 145 (1973); Angew. Chem. internat. Edit. *12*, 150 (1973). This work was supported by the Deutsche Forschungsgemeinschaft.

[2] This is a mixture of *(2a)* 60% and *(2b)* 40% which so far has not proved separable.

[3] $AgClO_4$, which is soluble in benzene, was used. There was no visible precipitation of AgCN.

[4] *R. Breslow*, *P. Gal*, *H. W. Chang*, and *L. J. Altmann*, J. Amer. Chem. Soc. *87*, 5139 (1965).

[5] On the basis of NMR analysis the reaction mixture may contain up to 5% of the *o*-isomer of *(7)* (cf. Ref. [1]); this could not be established with certainty because that isomer could not be separated.

[6] This chemical shift is, in our experience [1], characteristic of the methine proton of such Dewar-benzenes.

[7] This valence isomerization was followed by NMR spectroscopy of a $CDCl_3$ solution after removal of the benzene at the lowest possible temperature.

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[10] *W. Schmidt*, Tetrahedron Lett. *1972*, 581.

Influence of Ligands on Catalysts for the Heterogeneous Metathesis of Olefins

By *G. Henrici-Olivé* and *S. Olivé*[*]

In 1963 *Banks* and *Bailey*[1] reported the metathesis of olefins over molybdenum and tungsten catalysts on alumina supports. Straight-chain olefins were found to undergo conversion at 120–160 °C into homologs having longer chains and those having shorter chains, *e.g.*:

$$2CH_3{-}CH{=}CH_2 \rightleftarrows CH_2{=}CH_2 + CH_3{-}CH{=}CH{-}CH_3 \quad (1)$$

$$2CH_3{-}CH_2{-}CH{=}CH_2 \rightleftarrows CH_2{=}CH_2 + CH_3{-}CH_2{-}CH{=}CH{-}CH_2{-}CH_3 \quad (2)$$

Meanwhile the new reaction type has attracted wide interest[2–4].

We wish to report on modifications to the conventional molybdenum catalyst which increase its activity to such a degree that much lower working temperatures are required. We have chosen the metathesis of propene and 1-butene as test reactions [cf. eq. (1) and (2)].

Pseudo γ-alumina (particle diameter *ca.* 3 mm, surface area 299 m^2/g) was impregnated with aqueous ammonium molybdate; after evaporation of the solvent the catalyst was oxidized at 500 °C in an O_2 stream for 8 hours (catalysts marked ox in Table 1). In several cases the catalyst was subsequently reduced at 500 °C in a CO stream for 3 hours and flushed with argon before use (marked red in Table 1). The reduced catalysts are considerably more active, with both propene and 1-butene, under otherwise identical conditions (see runs 1—4 in Table 1).

The alumina was impregnated with ethanolic $Ti(OC_4H_9)_4$ solutions of varying concentrations; after evaporation of the solvent and oxidation (8 hours, 500 °C, O_2), molybdenum was applied to the same carrier and oxidized as described above. Finally the catalysts were activated with CO. Table 1 shows that the activity of the catalysts containing both metals is considerably higher than that of the catalysts containing either metal alone; the synergic effect of the titanium increases with increasing Ti content for a fixed Mo charge (see runs 5—8 and 10—13).

A combination of both effects, at suitable molybdenum charge and flow rate, allows conversions close to the equilibrium values[5] at moderate temperatures (*e.g.* run 13).

Whereas reaction (1) gives only C_2 and C_4 species, considerable amounts of C_3 and C_5 compounds are in-

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Table 1. Effect of pretreated molybdenum catalysts on reactions (1) and (2).

Run	Catalyst	$[Mo] \times 10^3$ [a]	Ti/Mo	Reaction	V[b]	T [°C]	Conversion (mol-%) [c]
1	ox	0.9	0	(1)	0.023	68	4.1
2	red	0.9	0	(1)	0.023	68	36.3
3	ox	0.9	0	(2)	0.3	55	1.2
4	red	0.9	0	(2)	0.3	55	9.3
5	red	0.1	0	(1)	0.21	68	0.8
6	red	0.1	9.5	(1)	0.21	68	4.5
7	red	0.1	19.0	(1)	0.21	68	7.8
8[d]	red	—	∞	(1)	0.21	68	0.04
9	red	0.1	0	(2)	0.24	68	0.3
10	red	0.1	1.9	(2)	0.24	68	3.4
11	red	0.1	9.5	(2)	0.24	68	11.5
12	red	0.1	19.0	(2)	0.24	68	22.4
13	red	0.8	3.3	(2)	0.03	55	59.5

[a] g-atom/g catalyst.
[b] Flow rate V in mol substrate/(min × g-atom Mo).
[c] Products in effluent other than substrate.
[d] $[Ti] = 1 \times 10^{-3}$ g-atom/g catalyst; no Mo.

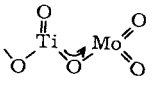
variably produced in reaction (2)[1, 6] whose formation is attributable to isomerization of both 1-butene and 3-hexene prior to metathesis. (Regarding the molecular weight distribution, see ref.[7].)

The oxidized catalysts are diamagnetic, the reduced ones paramagnetic. Table 2 and Figure 1 give the result of the magnetic susceptibility and EPR measurements.

Table 2. Magnetic data of reduced catalysts.

$[Mo] \times 10^3$ [g-atom/g cat.]	Ti/Mo	Spins/Mo	g-value
0.9	0	0.44	1.928
0.8	3.3	0.45	1.935

The magnetic data indicate that the titanium does not contribute to the paramagnetism of the catalyst, *i.e.* it is present in a diamagnetic form, presumably as Ti(IV). Evaluation of the magnetic susceptibility data gives 0.45 unpaired electrons per molybdenum in both cases, which is best interpreted assuming that about 50% of the molybdenum ions (originally present as MoO_3) are reduced to Mo(V) by the CO treatment. On the other hand, the different line shapes and g-values of the EPR signals indicate that the environment of the Mo ions changes when titanium is introduced. This, and the pronounced synergic effect of the titanium, lead to the conclusion that the active species in the bimetallic catalyst is a Ti(IV)-Mo(V) compound probably having an oxygen bridge, *e.g. (1)*.



(1)

MoO_3 is known to be strongly acidic: it dissolves readily in dilute alkali whereas TiO_2 is only poorly soluble in concentrated alkali[8]. It may therefore be assumed that TiO_2 acts as an electron donor toward the Mo(V) species. Both modification procedures (reduction of Mo(VI) to Mo(V) and formation of such a compound) would hence increase the electron density on Mo. If it is also borne in mind that the rate-determining step is not the actual metathesis between two olefin molecules coordinated to an Mo center but rather the desorption of the olefins[4], then the enhanced reactivity can be readily explained as a promotion of desorption: the increase in electron density at the Mo center weakens the coordinative bonding of the olefin[9].

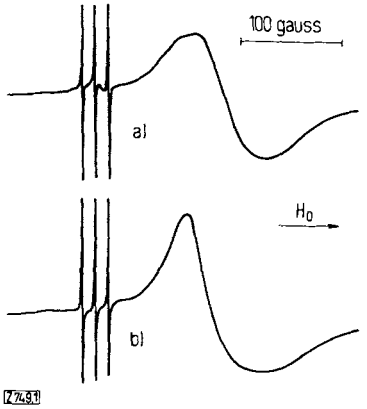


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Fig. 1. EPR signals of reduced catalysts. a) Ti/Mo = 0; b) Ti/Mo = 3.3 (three-line signal: field marker Fremy's salt).

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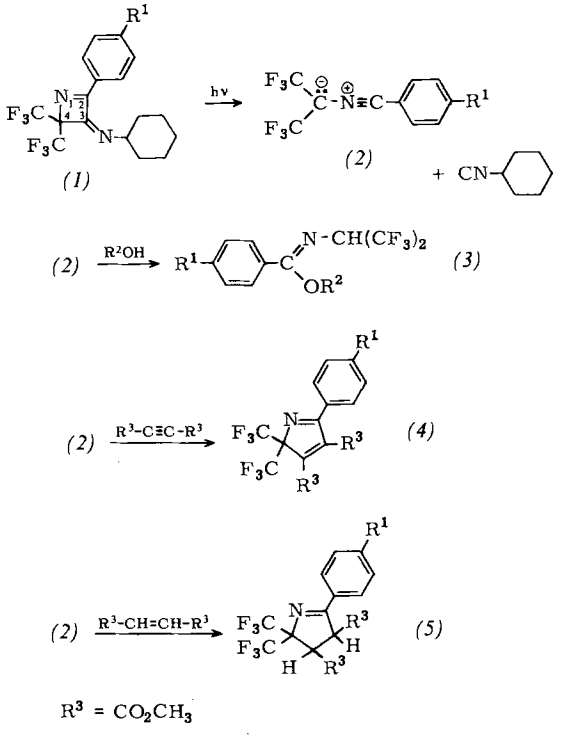
1,3-Dipolar Cycloreversion of 1-Azetines[**]

By *Klaus Burger, Willy Thenn,* and *Evi Müller*[*]

[3+1]-Cycloaddition of nitrile ylides[1] (obtained by thermolysis of 4,5-dihydro-1,3,5λ^5-oxazaphospholes[2]) to isocyanides leads to 1-azetines *(1)*[3,4]. This reaction is photochemically reversible.

On irradiation of *(1)* in benzene solution for several hours with a quartz lamp (Hanovia 450 watt) cycloelimination of isocyanide occurs. The nitrile ylide *(2)* formed can be trapped by alcohols as *N*-(hexafluoroisopropyl)benzimidic



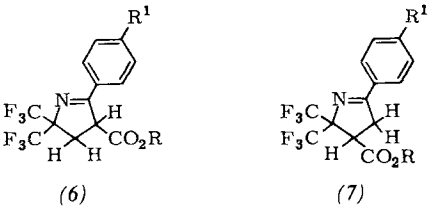
esters *(3)*, by dimethyl acetylenedicarboxylate as 2*H*-pyrroles *(4)*, and by dimethyl maleate or fumarate as 1-pyrrolines *(5)* (Table 1).

Table 1. Compounds of types *(3)*, *(4)*, and *(5)* prepared.

Cpd.	R^1	R^2	M.p. [°C] b.p. [°C/torr]	Yield [%]	*t* (h) [a]	IR [cm^{-1}]
(3a)	H	CH_3	78/12	40	21	1655[b]
(3b)	CH_3	CH_3	44/0.2	35	24	1655[b]
(3c)	Cl	CH_3	35/0.1	40	21	1655[b]
(3d)	F	CH_3	79/12	33	30	1655[b]
(3e)	H	C_2H_5	86/12	44	20	1660[b]
(3f)	Cl	C_2H_5	41/0.1	43	25.5	1655[b]
(4a)	H	—	97	25	41	1730, 1715, 1615[c]
(4b)	CH_3	—	58	23	24	1740, 1725, 1625[c]
(5a)	H	—	75	35	26.5	1730, 1615[c]
(5b)	CH_3	—	92	40	25	1735, 1615[c]

[a] *t* = time of irradiation. [b, c] Measured as [b] film, [c] KBr disk, on a Perkin-Elmer Infracord instrument.

If acrylic esters are used as dipolarophile, then the ylide *(2)* yields the isomers *(6)* and *(7)*. Table 2 gives the isomer ratios determined by NMR spectroscopy. The results are comparable with those found previously on thermolysis and photolysis of 4,5-dihydro-1,3,5λ^5-oxazaphospholes in the presence of acrylic esters[1].



(6) *(7)*

Table 2. Ratios of isomers formed on reaction of *(2)* with acrylic esters.

(6)+(7)	R^1	R	*(6)*:*(7)*
(a)	H	CH_3	58:42
(b)	CH_3	CH_3	63:37
(c)	Cl	CH_3	56:44
(d)	H	C_2H_5	57:43
(e)	CH_3	C_2H_5	65:35
(f)	Cl	C_2H_5	63:37

Formation of the same products and almost identical isomer ratios indicate occurrence of the same intermediate for photolysis of 1-azetines *(1)* and thermolysis or photolysis of 4,5-dihydro-1,3,5λ^5-oxazaphospholes.

The nature of the products rules out electrocyclic ring fission (cleavage of the bond between C3 and C4) which was found for cyclobutenones[5]. Ring fission between C2 and C3 and subsequent decomposition to nitrile ylide and isocyanide — if the intermediate has a longer life — should, on reaction with methanol, give different trapping products and different ratios of the isomers produced by the addition. Thus a simultaneous or nearly synchronous bond cleavage between C2 and C3, and between C3 and C4, appears probable, which corresponds to a cheletropic [3+1]-cycloelimination on *Woodward* and *Hoffmann*'s classification[6].

Ethyl p-chloro-N-(hexafluoroisopropyl)benzimidate (3f):

2-(*p*-Chlorophenyl)-3-cyclohexylimino-4,4-bis(trifluoromethyl)-1-azetine[4] (7.9 g, 20 mmol) and anhydrous ethanol (50 ml) are irradiated in anhydrous benzene (250 ml) for 25.5 h by a quartz lamp (Hanovia 450 watt). After removal of the excess of alcohol, the solvent, and the cyclohexyl isocyanide formed, the residue is fractionated twice through a small column, giving a 43% yield (2.8 g) of *(3f)*.

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[1] For nitrile ylides see *K. Burger* and *J. Fehn*, Chem. Ber. *105*, 3814 (1972).

[2] *K. Burger, J. Fehn,* and *E. Moll*, Chem. Ber. *104*, 1826 (1971).

[3] *K. Burger* and *J. Fehn*, Angew. Chem. *84*, 35 (1972); Angew. Chem. internat. Edit. *11*, 47 (1972).

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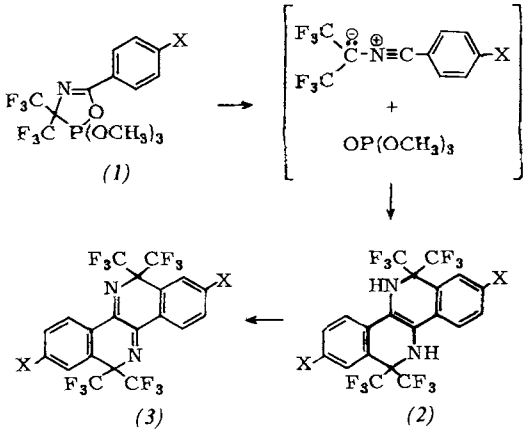
A New Type of Dimerization of Nitrile Ylides[***][1]

By *Klaus Burger*, *Kurt Einhellig*, and *Georg Süss*[*], together with *Alfred Gieren*[**]

We reported recently on cycloadditions[2] of the nitrile ylides produced by thermolysis or photolysis of 4,5-dihydro-1,3,5λ⁵-oxazaphospholes[****] *(1)*. On thermolysis of *(1)* in anhydrous xylene at 140 °C in absence of a dipolarophile, dimers *(2)* are formed with cycloelimination of phosphoric acid esters. The dimers are readily oxidized and with mercury(II) acetate afford excellent yields of 6,12-dihydro-6,6,12,12-tetrakis(trifluoromethyl)dibenzo-[*c*,*h*][1,5]naphthyridines *(3)*. The photolysis of *(1)* in benzene leads to *(3)* directly but in lower yields. IR, NMR, UV, and mass spectral data of *(3)* are available (Table 1); decision upon structure *(3)* followed from X-ray structure analysis[3].



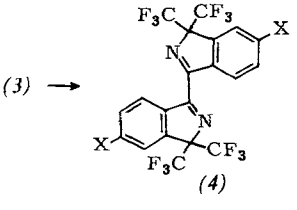
(1) *(3)* *(2)*

Table 1. Properties of *(3)* and *(4)*.

Cpd.	X	Yield [%]	M.p. [°C]	IR [cm⁻¹] [c]
(3a)	H	45[a] 90[b]	157	1628, 1600
(3b)	CH_3	36[a] 93[b]	227	1630, 1600
(3c)	OCH_3	30[a] 80[b]	213—213	1620, 1600
(4a)	H	90[d]	176	1600, 1538
(4b)	CH_3	95[d]	207	1610, 1535

[a] Yield referred to *(1)*.
[b] Yields referred to *(2)*.
[c] Measurements for KBr disks by a Perkin-Elmer Infracord instrument.
[d] Yields based on *(3)*.

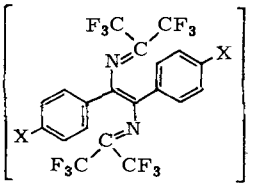
Heating the product *(3)* in methanolic KOH in a sealed tube at 120—130 °C converts it into 1,1,1′,1′-tetrakis-(trifluoromethyl)-3,3′-bi(1*H*-isoindole) *(4)* in high yields. *(3a)* and *(4a)*, and *(3b)* and *(4b)*, give barely distinguishable mass spectra. The electron band of longest wavelength appears at almost the same wavelength (for IR spectra see Table 1). The constitution of *(4)* was solved by X-ray structure analysis[4].



(3) → *(4)*

The dimerization products of nitrile ylides previously reported have been dihydropyrazines (readily convertible into pyrazines[5, 6]), 1,3-diazabicyclo[3.1.0]hex-3-enes[6, 7], imidazoles[6–8], and pyrimidines[7].

Since benzoylphenylcarbene (obtained from 4,5-diphenyl-1,3,2λ⁵-dioxaphosphole by thermolysis) dimerizes to dibenzoylstilbene[9], we postulate an analogous initial reaction step. The 2-azahexatriene system of *(5)* undergoes the thermally allowed disrotatory ring closure with subsequent [1.5]-sigmatropic H shift[10]. The reaction sequence is repeated in the other half of the molecule. The resulting enediamine *(2)* is extremely readily oxidized, so that *(2)* always contains small amounts of *(3)*.



(5)

The conversion *(3)* → *(4)* is merely an opening of the six-membered ring system and formation of the five-membered ring system; it proves the structure of *(3)*.

Experimental:

(1a) (9.85 g, 25 mmol) is heated in anhydrous xylene (50 ml) for 16 h at 140 °C. Then, after cooling, the solvent and trimethyl phosphate formed are distilled off in a vacuum. The residual yellow solid is digested with a little cold methanol, filtered off, and refluxed in methanol with an excess of mercury(II) acetate for 5 h. The mixture is then evaporated to dryness and the residue is digested in a little chloroform; most of the mercury(I) acetate remains undissolved. Recrystallization from methanol gives 45% (2.9 g) of *(3a)*.

(3a) (2.54 g, 5 mmol) is heated with methanol (200 ml) and concentrated KOH (5 ml) in a sealed tube for 48 h at 120—130 °C. After cooling, crystallization begins and is completed by addition of water. Yield 2.3 g, 90%; m.p. 176 °C (from methanol).

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[***] This work was supported by the Stiftung Volkswagenwerk.

[****] Previously called 4,5-dihydro-1,3,5-oxazaphosph(v)oles.

[1] Reactions of 4,5-Dihydro-1,3,5λ⁵-oxazaphospholes, Part 7. Reported at the 4th European Symposium on Fluorine Chemistry, August 1972, Ljubljana, Yugoslavia.—Part 6: [2e].

[2] a) *K. Burger* and *J. Fehn*, Angew. Chem. *83*, 761, 762 (1971); Angew. Chem. internat. Edit. *10*, 728, 729 (1971); b) Tetrahedron Lett. *1972*, 1263; c) Chem. Ber. *105*, 3814 (1972); d) Angew. Chem. *84*, 35 (1972); Angew. Chem. internat. Edit. *11*, 47 (1972); e) *K. Burger*, *J. Fehn*, and *E. Müller*, Chem. Ber. *106*, 1 (1973).

[3] *A. Gieren*, *K. Burger*, and *K. Einhellig*, Angew. Chem. *85*, 171 (1973); Angew. Chem. internat. Edit. *12*, 157 (1973).

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[9] *T. Mukaiyama* and *T. Kumamoto*, Bull. Chem. Soc. Jap. *39*, 879 (1966); Chem. Abstr. *65*, 7085 h (1966).

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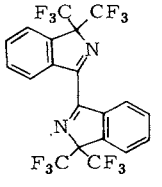
X-Ray Structure Analysis of 1,1,1′,1′-Tetrakis-(trifluoromethyl)-3,3′-bi(1*H*-isoindole)

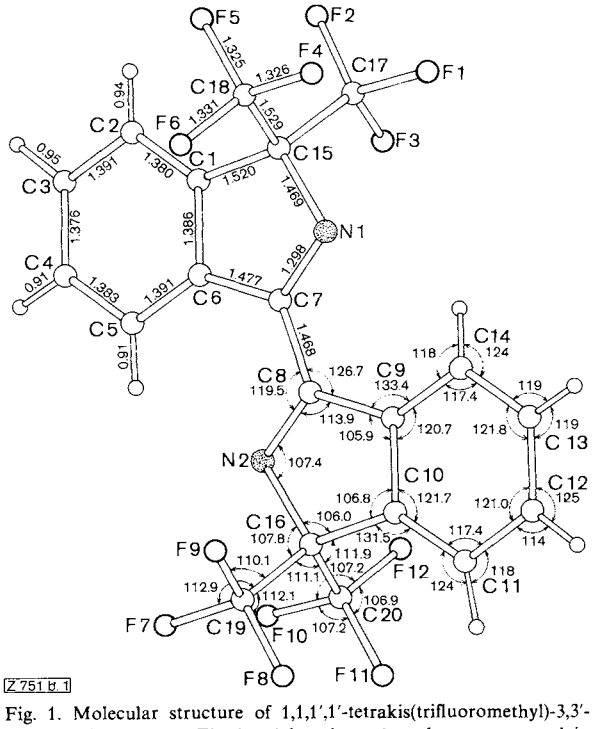
By *Alfred Gieren*[*], together with *Klaus Burger* and *Kurt Einhellig*[**]

We have carried out an X-ray structure analysis of 1,1,1′,1′-tetrakis(trifluoromethyl)-3,3′-bi(1*H*-isoindole) *(1)* in order to solve its structure and mode of formation. The analysis led to the detection of a novel type of dimerization of nitrile ylides[1].

Suitable single crystals were obtained from methanolic solution. Space group Pbca; $a = 16.55_0$, $b = 21.76_9$, $c = 10.64_7$ Å; $d_{obs} = 1.73_7$ g cm^{-3}; 1 molecule/asym. unit ($d_{calc} = 1.74_6$ g cm^{-3}). 3631 independent reflections were measured on a Siemens diffractometer with $Cu_{K\alpha}$ radiation (695 not observed, $I \leq 2\sigma_I$; $\vartheta \leq 70°$, $\vartheta/2\vartheta$ scan, 5-point measurements).



(1)



Z 751 b 1

Fig. 1. Molecular structure of 1,1,1′,1′-tetrakis(trifluoromethyl)-3,3′-bis(1*H*-isoindole) *(1)*. The bond lengths and angles are averaged in accord with 2/m symmetry. Standard deviations of the bond lengths and angles (without averaging in accord with 2/m) amounted on the mean to 0.014 Å and 0.9° (without C—H: 0.12 Å or C—C—H: 8°).

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The signs of 290 structure factors were determined by direct methods[2]. The positions of all the atoms (except H) could be seen in a *E*-Fourier synthesis. Least squares refinement, first with isotropic, then with anisotropic temperature factors, was carried out to an *R* value of 10.2%. Thereafter, the H atoms found in a difference Fourier synthesis were included in the refinement. Towards the end of the refinement all the data were corrected for absorption by an experimental method[3]. Structure factors with $|\Delta F| > 5$ (in the last cycle 43) were no longer used for calculation of shift. Convergence occurred at $R = 6.2\%$ (*R* value without 28 reflections with $\Delta F < -10$: 4.7%).

To a first approximation the molecule *(1)* (Fig. 1) has 2/m symmetry. Bond lengths and bond angles do not deviate significantly from this symmetry. The two isoindole rings are planar and only slightly twisted relative to one another around the C7—C8 bond (angle between the best planes: 2.9°). The almost planar, centrosymmetrical conformation of the 1,4-diaza-1,3-butadiene system explains the absence of the IR band at 1628 cm^{-1} ($\nu_{C=N}$)[1].

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German version: Angew. Chem. *85*, 170 (1973)

[1] *K. Burger, K. Einhellig, G. Süss*, and *A. Gieren*, Angew. Chem. *85*, 169 (1973); Angew. Chem. internat. Edit. *12*, 156 (1973).

[2] Program by *K. Zechmeister*; *W. Hoppe, J. Gassmann*, and *K. Zechmeister* in *F. R. Ahmed*: Crystallographic Computing. Munksgaard, Copenhagen, 1970, p. 26.

[3] *R. Huber* and *G. Kopfmann*, Acta Crystallogr. *A 25*, 143 (1969).

X-Ray Structure Analysis of 6,12-Dihydro-6,6,12,12-Tetrakis(trifluoromethyl)dibenzo[*c*,*h*]-[1,5]naphthyridine

By *Alfred Gieren*[*], together with *Klaus Burger* and *Kurt Einhellig*[**]

We have carried out an X-ray structure analysis of 6,12-dihydro-6,6,12,12-tetrakis(trifluoromethyl)dibenzo[*c*,*h*][1,5]naphthyridine in order conclusively to prove its structure and formation by a new type of dimerization of nitrile ylides[1].

The single crystals obtained from methanolic solution are monoclinic. Space group $P2_1/b$; $a = 13.42_9$, $b = 13.03_8$, $c = 11.10_5$ Å, $\gamma = 103.2_9°$; $d_{obs} = 1.75$ g cm^{-3}; 1 molecule/asym. unit ($d_{calc.} = 1.77$ g cm^{-3}). 3586 independent reflections (400 not observed, $I \leq 2\sigma_I$; $\vartheta \leq 70°$, $\vartheta/2\vartheta$ scan, 5 point measurements) were recorded on a Siemens diffractometer with $Cu_{K\alpha}$ radiation.

Positions of all the atoms (except H) were found in an *E*-Fourier synthesis calculated with 298 structure factors which were phased by direct methods[2]. After least-squares refinement, first with isotropic and then with anisotropic temperature factors, all the H atoms could be found in a difference Fourier synthesis at an *R* value of 10.1%. The refinement was continued with inclusion of the H atoms; towards the end an experimental absorption correction was carried out[3]. Structure factors with

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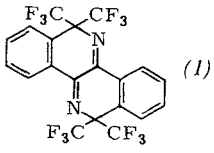
$|\Delta F| > 5$ (34 in the last cycle) were no longer included in shift calculation. The refinement converged at R = 6.8% (R value without 20 reflections with $\Delta F < -10$: 5.4%).



(1)

Angles [°]

C16—C19—F7: 112.9	C16—C20—F10: 112.5
C16—C19—F8: 112.1	C16—C20—F11: 112.6
C16—C19—F9: 109.8	C16—C20—F12: 110.2
C17—C15—C18: 111.1	

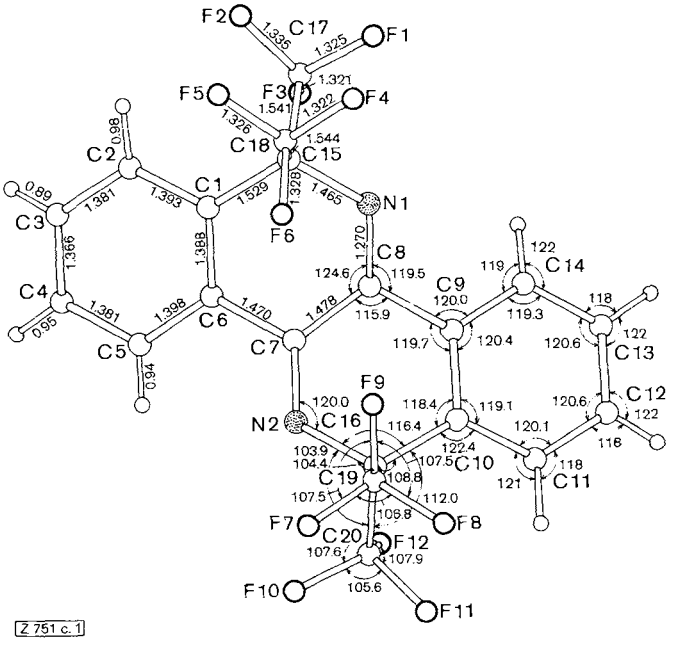


Fig. 1. Molecular structure of 6,12-dihydro-6,6,12,12-tetrakis(trifluoromethyl)dibenzo[c,h][1,5]naphthyridine *(1)*. The bond lengths and angles were determined with consideration of two-fold molecular symmetry. The standard deviations of the bond lengths and angles (without averaging on the basis of the two-fold symmetry axis) had mean values of 0.014 Å or 0.9° (without C—H: 0.11 Å, or without C—C—H: 6°).

The molecule *(1)* (Fig. 1) has a two-fold symmetry axis perpendicular to the central C7—C8 bond. The benzene rings are planar, but the heterocycles of the naphthyridine system are in boat form, which *inter alia* leads to the π-orbitals at C-6, C-7, and C-8 having a twist around C7—C8 (N2—C7—C8—N1: 164.7°) and around C6—C7 (C5—C6—C7—N2: 14.3°). Further the twist at C7—C8 explains the appearance of the IR band at 1628 cm^{-1}[1].

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[1] a) *K. Burger, K. Einhellig, G. Süss,* and *A. Gieren,* Angew. Chem. *85*, 169 (1973); Angew. chem. internat. Edit. *12*, 156 (1973); b) *A. Gieren, K. Burger,* and *K. Einhellig,* Angew. Chem. *85*, 170 (1973); Angew. Chem. internat. Edit. *12*, 157 (1973).

[2] Program by *K. Zechmeister; W. Hoppe, J. Gassmann,* and *K. Zechmeister* in *F. R. Ahmed:* Crystallographic Computing. Munksgaard, Copenhagen 1970, p. 26.

[3] *R. Huber* and *G. Kopfmann,* Acta Crystallogr. *A 25*, 143 (1969).

Crystal Structure of Allenedicarboxylic Acid[***]

By *Leslie Leiserowitz* and *Franz Nader*[*]

The interest in both the stereochemistry and chemical reactivity of cumulenes warrants thorough and systematic X-ray studies of this class of compounds. The only investigation of this kind to be published so far concerned tetraphenylhexapentaene[1] and yielded gross structural features only, because of two-dimensional diffraction data. Nevertheless, electron diffraction studies have been carried out on allene[2a,b] and butatriene[3].

We have undertaken the structure analysis of a derivative of allene, the simplest molecule in the cumulene series. We chose allenedicarboxylic acid (glutinic acid) because of its easy preparation[4] and the restricted thermal vibrations expected in the crystalline phase.

Single crystals of the compound were obtained by slow evaporation of acetic acid solutions[****]. Crystallographic data: orthorhombic; $a = 15.108$ Å, $b = 8.214$, $c = 4.527$; space group: $Pna2_1$, $Z = 4$; $d_{exp} = 1.53$, $d_{calc} = 1.514$ g/cm³.

The structure was solved by a direct method[5] using the multi-solution technique[6]. The positions of the hydrogen atoms were obtained from the difference map. The refinement with 764 independent reflections (of which 150 were treated as unobserved) yielded a final agreement factor of $R = 4.0\%$.

Bond lengths and bond angles are shown in Fig. 1. The length of the C=C double bond of the cumulene system is without doubt shorter than that of the isolated or conjugated C=C double bond (*ca.* 1.33—1.34 Å). The same conclusion was reached in the electron diffraction study of allene[2b] which yielded a C=C bond somewhat longer than that of the present X-ray study (1.311 Å *vs.* 1.298).

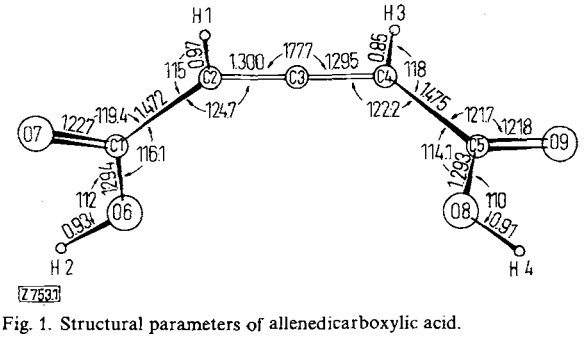

Fig. 1. Structural parameters of allenedicarboxylic acid.

That the carbonyl groups and the double bonds are in conjugation is indicated by the shortness of the carbon single bond joining them (1.474 Å). Whereas the bond lengths in the two halves are in good agreement the bond angles show distinct differences beyond the limit of probable error of 0.3°.

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[***] Cumulenes, Part 1.

[****] In ethanol or water solutions partial decarboxylation combined presumably with dimerization occurs. One obtains monoclinic crystals of space group $P2_1/c$. From the measured density the molecular weight is calculated to *ca.* 172. In ethanol at −15°C however, this reaction is suppressed and one can obtain single crystals of allenedicarboxylic acid by slow evaporation.

The allene bonds are not completely linear. The small deviation (2.3°) is presumably due to steric interactions between the carboxyl groups and the central allene carbon atom (C-3). The planes of the two carboxyl groups are—as expected—perpendicular to each other. The carboxyl groups are each slightly twisted (*ca.* 2°) out of the plane of the allene system.

The conformation of the molecule surprisingly shows an *anti*-planar arrangement of carbonyl groups and allene double bonds. The *syn*-planar disposition is usually found in α,β-unsaturated carboxylic acids and derivatives thereof[7, 8].

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[6] *G. Germain* and *M. M. Woolfson*, Acta Crystallogr. *B 24*, 91 (1968); see also *H. W. Kaufman* and *L. Leiserowitz*, Acta Crystallogr. *B 26*, 442 (1970).

[7] *L. Leiserowitz* and *G. M. J. Schmidt*, Acta Crystallogr. *18*, 1058 (1965).

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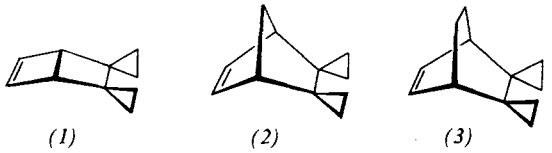
[2+2]- and [2+4]-Cycloadditions of Bicyclopropylidene[**]

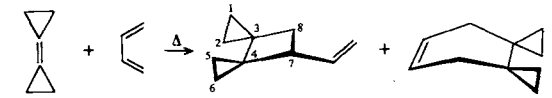
By *Dieter Kaufmann* and *Armin de Meijere*[*]

Methylenecyclopropane[1] and substituted methylenecyclopropanes[2,3] undergo thermal dimerizations in analogy to fluoroalkenes, yielding cyclobutane derivatives. Dichloromethylenecyclopropane reacts also with 1,3-butadiene exclusively by [2+2]-cycloaddition[4]. Potential [2+4]-cycloadducts such as *(1)*, *(2)*, and *(3)* of the bicyclopropylidene system *(4)* to cyclic 1,3-dienes are of particular interest with regard to possible "through-space" electronic interaction between the Walsh orbitals[5] of the cyclopropane ring and the π-electrons of the double bond. We have therefore investigated the question whether [2+4]-cycloadducts are formed on thermal reaction of *(4)* with 1,3-dienes.

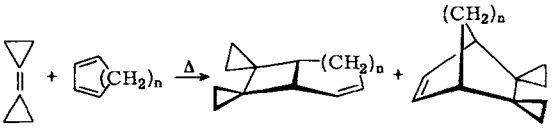


(1) *(2)* *(3)*

Bicyclopropylidene *(4)*[6] was heated with a 4- to 8-fold molar excess of 1,3-butadiene *(5)*, cyclopentadiene *(8)*, or 1,3-cyclohexadiene *(9)* and a trace of hydroquinone in sealed glass ampoules at 150–180°C. The crude mixture of products was analyzed by gas chromatography; a combination of gas chromatography and mass spectrometry (GC-MS) initially revealed the components that had molecular weights expected of the respective cycloadducts of *(4)*. The individual components were then isolated pure by preparative gas chromatography; their structural elucidation was based mainly on NMR-spectroscopic data[7]. The reaction conditions and relative yields are collected in Table 1.



(4) *(5)* *(6)* *(7)*



(4) *(8)*, n = 1; *(9)*, n = 2 *(10)*, n = 2 *(2)*, n = 1; *(3)*, n = 2

Table 1. Conditions and yields in the reaction of *(4)* with 1,3-dienes.

Diene	Reaction condns. T[°]	t[h]	Products, rel. yields [2+2]-adduct	[2+4]-adduct	Total yield [b]
(5)	180	12	*(6)* 92%	*(7)* 8%	54%
(8)	150	10	[a]	*(2)* >97%	16%[c]
(9)	170	11	*(10)* 78%	*(3)* 22%	50%

[a] It was not possible to detect a product corresponding to *(10)* but with $n=1$.
[b] Total yield of products isolated by gas chromatography.
[c] In this reaction the bicyclopropylidene did not undergo complete conversion.

Cyclopentadiene *(8)* gave only one product of mass number 146; no further component of that mass number could be detected in the crude product mixture by GC-MS. The NMR spectrum (CCl_4) of this product showed a multiplet centered at $\tau=9.88$ (8 cyclopropyl protons), $\tau=7.88$ (2 bridgehead protons) and $\tau=3.80$ (2 olefinic protons), together with an AB line system centered at $\tau=8.20$ (2 methylene protons); the number and coupling patterns of the signals indicate the structure bicyclo[2.2.1]hept-2-ene-5,6-dispirocyclopropane *(2)*[17].

When *(4)* was treated with 1,3-cyclohexadiene *(9)* two products of mass number 160 were formed as well as dimeric cyclohexadiene (also mass number 160). The NMR spectrum ($CDCl_3$) of one of the components showed multiplets centered at $\tau=9.95$ (8 cyclopropyl protons), $\tau=8.79$, 8.15 (2 protons each of the ethano bridge, respectively *endo* and *exo* to the double bond), $\tau=8.47$ (2 bridgehead protons), and $\tau=3.66$ (2 olefinic protons); these signals were identical with those of a sample of bicyclo[2.2.2]oct-2-ene-5,6-dispirocyclopropane *(3)* synthesized by an independent route[8]. The spectrum (CCl_4) of the main component, showing multiplets at $\tau=9.83$ (8 cyclopropyl protons), $\tau=8.47$, 7.98 (2 methylene protons each), $\tau=7.37$, 7.07 (1 methine proton each), and $\tau=4.48$, 4.11

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(1 olefinic proton each) is consistent only with the structure of bicyclo[4.2.0]oct-2-ene-7,8-dispirocyclopropane *(10)*.

1,3-Butadiene, which is a diene not fixed in the *cis*-configuration, gave two cycloadducts of molecular weight 134. A component forming only 8% of the total yield was, according to its NMR spectrum and gas-chromatographic retention time, identical with authentic dispiro[2.0.2.4]-dec-8-ene *(7)*[11]. The main product gives a NMR spectrum (CCl_4) with signals at $\tau = 9.75$ (m, 8 cyclopropyl protons), $\tau = 7.64$ (AB system, split into doublets, 2 cyclobutylmethylene protons), $\tau = 6.93$ (q, 1 cyclobutyl-methine proton), $\tau = 5.21$, 5.07, 4.15 (ABC line system, 3 vinyl protons), and thus has the structure 7-vinyldispiro[2.0.2.2.]-octane *(6)*.

Attempts to react *(4)* with cyclobutadiene produced *in situ*[12] in order to obtain bicyclo[2.2.0]hex-1-ene-5,6-dispirocyclopropane *(1)* have so far been without success. No unchanged *(4)* could be recovered, but no component of the expected molecular weight 132 could be detected in the crude product by GC-MS.

According to the above findings bicyclopropylidene *(4)* behaves differently from dichloromethylenecyclopropane[4] in reactions with conjugated dienes. Although it appears to add preferentially by a diradical mechanism, it can nevertheless also react by way of the transition state of a synchronous Diels-Alder reaction, as is proved by the appearance of the [2+4]-adduct *(7)*[13,14].

The question of through-space electronic interaction between the cyclopropane rings and the double bonds is being studied for compounds of types *(2)* and *(3)* by means of photoelectron spectroscopy[16].

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German version: Angew. Chem. *85*, 151 (1973)

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[2] *W. R. Dolbier jr.*, *D. Lomas*, and *P. Tarrent*, J. Amer. Chem. Soc. *90*, 3594 (1968).

[3] *P. Le Perchec* and *J. M. Conia*, Tetrahedron Lett. *1970*, 1587.

[4] *P. D. Bartlett* and *R. C. Wheland*, J. Amer. Chem. Soc. *94*, 2145 (1972).

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[6] Prepared from cyclopropene as described by *A. J. Schipperijn*, Rec. Trav. Chim. Pays-Bas *90*, 1110 (1971).

[7] All new compounds gave satisfactory C/H analyses and molecular weights (determined by mass spectrometry).

[8] Prepared from the Diels-Alder adduct of maleic anhydride to dispiro[2.0.2.4]deca-7,9-diene [9] by hydrogenation of the double bond and subsequent oxidative bisdecarboxylation of the dicarboxylic acid with the aid of lead tetraacetate [10].

[9] *A. de Meijere*, Angew. Chem. *82*, 934 (1970); Angew. Chem. internat. Edit. *9*, 899 (1970).

[10] *A. de Meijere* and *D. Kaufmann*, unpublished work.

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[13] Cf. *P. D. Bartlett*, Pure Appl. Chem. *16*, 187 (1968).

[14] It was established that the [2+2]-cycloadduct *(6)* does not rearrange to *(7)* under the reaction conditions [15].

[15] Cf. *J. J. Eisch* and *G. R. Husk*, J. Org. Chem. *31*, 589 (1966).

[16] In collaboration with *M. Klessinger* and *K. Wilhelm*, Münster.

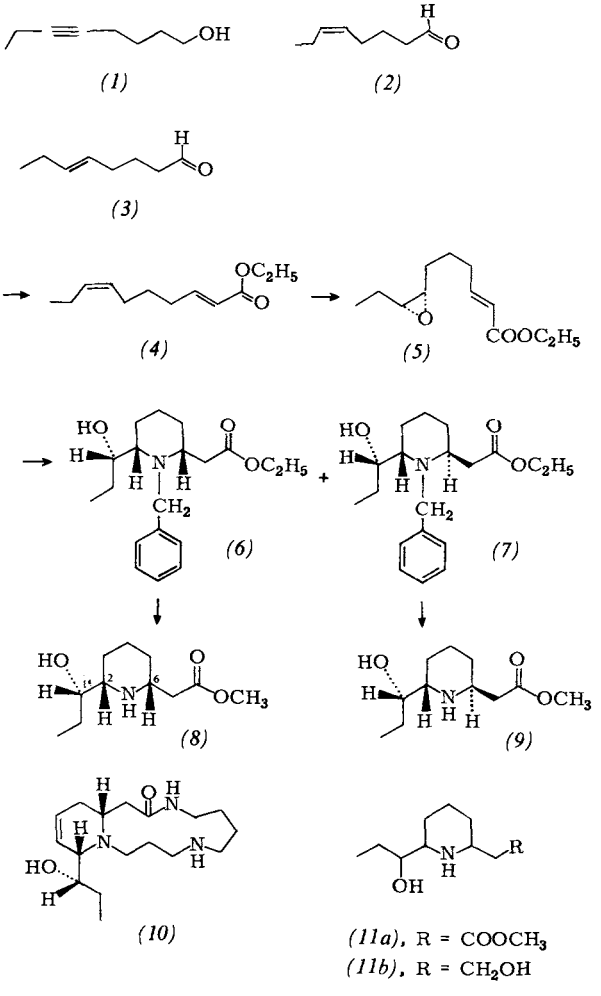
[17] *Note added in proof* (Jan. 11, 1970): *(2)* has also been synthesized by an independent route starting from the Diels-Alder adduct of ethylenetetracarboxylic dianhydride and cyclopentadiene (*J. Sauer*, *B. Schröder*, and *A. Mielert*, Chem. Ber. *100*, 315 (1967)) in analogy to the synthesis of *(7)* [11].

Synthesis of (±)-Dihydropalustraminic Acid

By *Peter Wälchli* and *Conrad Hans Eugster*[*]

In palustrine *(10)*, the poisonous main alkaloid of *Equisetum palustre* L. (marsh horsetail), we recognized in 1960 the first member of the spermidine alkaloids[1]. The key substance in the determination of its structure was the methyl dihydropalustraminate *(11a)* obtained therefrom by Hofmann degradation[2]. The synthesis described below confirms the constitutional formula proposed and also clarifies the steric relations:

5-Hexyn-1-ol[3] was ethylated *via* its pyranyl ether by ethyl bromide ($NaNH_2/NH_3$-ether), and the 5-octyn-1-ol *(1)* obtained was reduced catalytically and then oxidized by Collins' method[4] to *cis*-5-octen-1-al *(2)*. The ester *(4)* was then formed by olefination of the anion of ethyl (diethylphosphino)acetate (NaH-benzene) and was epoxidized on the non-conjugated double bond to give *(5)*. Treatment with benzylamine next caused opening of the oxide (*threo*-amino alcohol) and ring closure to the *cis*- *(6)* and *trans*-piperidine *(7)*, which were separated on a preparative scale by chromatography on alumina (Alox). On



hydrolysis and transesterification we then obtained the (±)-compounds corresponding to *(8)* and *(9)*, respectively. Their stereochemistry followed from NMR measure-

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ments (cf. Ref.[5]) and lactonization experiments[6]. The synthetic (±)-*threo-cis*-methyl ester *(8)* [m.p. (hydrochloride) 176.4—177 °C] was spectroscopically and chromatographically identical with the (−)-methyl ester [m.p. (hydrochloride) 185 °C] obtained by degradation of the alkaloid.

Analogous reactions with *trans*-5-octenal *(3)* have led to synthesis of the *erythro-cis*- and the *erythro-trans*-compound *(11a)*; these stereoisomers differ significantly from *(8)* in their NMR and IR spectra.

The (2*S*,6*R*,1′*S*)-configuration of (−)-*(8)* follows unambiguously from the chiroptical data for (−)-*(8)* and (−)-*cis-(11b)*[7] together with the *threo*-configuration that has now been proved. Thus palustrine has structure *(10)*.

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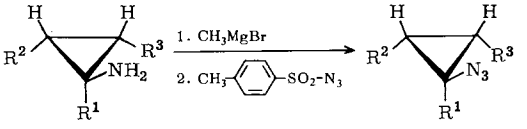
The Thermolysis of Cyclopropyl Azides[1]

By *Günter Szeimies*, *Udo Siefken*, and *Rolf Rinck*[*]

Cyclopropyl azides were unknown until very recently when some representatives of this class of compounds were synthesized by special reactions[2–4].

In the nitrogen-transfer reaction from *p*-toluenesulfonyl azides to anions of cyclopropylamines[5] we have found a more general method of preparing cyclopropyl azides.

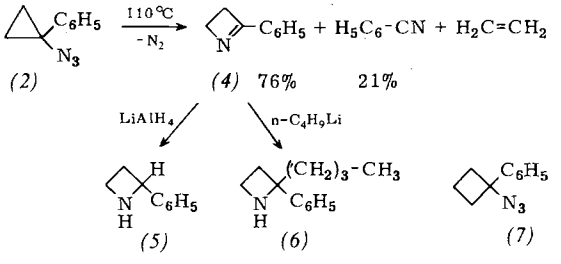
Thermal removal of nitrogen from the cyclopropyl azides *(1)*—*(3)* can be effected between 100 and 120 °C. For example, after 2 h in boiling toluene, *(2)* yielded 76% of 2-phenyl-1-azetine[7] *(4)* [NMR signals of the four-membered ring protons in carbon tetrachloride at 60 MHz: triplets (each 2 protons) at $\tau = 6.75$ and 6.15, $J = 3.5$ Hz; IR: C=N at 1568 cm^{-1}]. Reduction by $LiAlH_4$ converts



(1) - *(3)*

Compound	Yield [%] [6, 7]	B.p. [°C/torr]
(1), $R^1=R^3=H$, $R^2=C_6H_5$	36	45—50/0.003
(2), $R^1=C_6H_5$, $R^2=R^3=H$	40	45—48/0.001
(3), $R^1=H$, $R^2+R^3=-(CH_2)_4-$ [8]	21	35—38/0.01

(4) into 2-phenylazetidine *(5)*[7], and addition of butyllithium into 2-butyl-2-phenylazetidine *(6)*[7]; additionally, thermolysis of *(2)* affords 21% of benzonitrile and ethylene, of which the latter was identified as 1,2-dibromoethane.



(2) *(4)* *(5)* *(6)* *(7)*

Nitrogen cleavage from *(1)* in *o*-dichlorobenzene at 110 °C gave, together with styrene (57%) and hydrogen cyanide, a rapidly polymerizing oil that we have not yet been able to purify. Thermolysis of *(3)* in carbon tetrachloride in a sealed tube at 120 °C led to 90% of cyclohexene and a small amount of a resin.

Table 1. Rate constants of the azide thermolysis in *o*-dichlorobenzene [9].

Azide	Concn. [mol/l]	Temp. [°C]	$k_1 \times 10^4$ [s^{-1}]	E_A [kcal/mol]	$\Delta H^{\neq}$ [kcal/mol]	$\Delta S^{\neq}$ [cal mol^{-1} deg^{-1}]
(1)	0.0470	112.8	3.28			
	0.0470	126.1	12.3	30.5	29.7	2.0
	0.0470	135.2	29.2			
(2)	0.0476	102.5	3.12			
	0.460	102.5	3.20	28.9	28.2	0.0
	0.0476	112.7	8.70			
(3)	0.0460	100.0	2.31			
	0.0460	112.7	8.10	28.6	27.8	−0.6
	0.0460	120.0	16.4			
(7)	0.0562	150.0	1.04			
	0.0562	165.0	4.25	34.2	33.3	1.1
	0.0562	175.0	10.0			

It is noteworthy that the thermolysis temperature of the cyclopropyl azides is much lower than that of alkyl azides. Table 1 gives the first-order rate constants and the activation parameters of the thermal decomposition of the azides *(1)*, *(2)*, and *(3)* and of 1-phenylcyclobutyl azide *(7)*.

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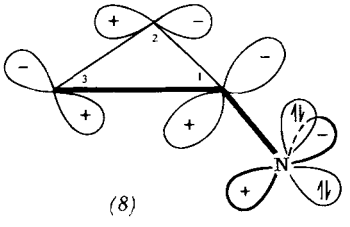
An activation energy of 38.5 kcal/mol[10] is required for removal of nitrogen from isopropyl azide, and of 47.5 kcal/mol for that from cyclohexyl azide[11]. What makes cyclopropyl azides so labile thermally? Loss of the three-membered ring strain cannot explain this great acceleration of the removal of nitrogen from three-membered ring azides: assuming comparable transition states, the four-membered ring azide *(7)* should decompose faster than the corresponding three-membered ring azide *(2)* if loss of ring strain has a decisive effect on the energy of the activation complex[12] since the cyclopropane and cyclobutane rings have approximately the same ring strains of 27.1 kcal/mol and 26.2 kcal/mol, respectively[13], whilst the azetine system which is the main thermolysis product of the three-membered ring azide should be considerably more strained than the 1-pyrroline system which is the thermolysis product of the four-membered ring azide. The activation enthalpy of thermolyis of the cyclobutyl azide *(7)* is about 5 kcal/mol greater than that of the cyclopropyl azide *(2)*, corresponding to a rate ratio of 1:525 at 102.5 °C, and this indicates that the cyclopropane ring is not broken to an appreciable extent in the rate-determining step of nitrogen elimination. Removal of nitrogen from the cyclopropyl azide should thus not be wholly synchronous with ring expansion and cheletropic elimination[14], but the reactions occur one after the other.

With this in mind we see a possible explanation of the considerable facilitation of removal of nitrogen from cyclopropyl azides by the electron donor effect of the cyclopropane system to the empty p orbital of the nitrene nitrogen in the orbital combination represented in *(8)*, the transition state being able to profit therefrom: the occupied asymmetric Walsh orbital[15] of the cyclopropane can fill the electron deficiency on the nitrene nitrogen caused by nitrogen elimination[16].



(8)

This "vertical stabilization"[17] of the nitrene nitrogen by the cyclopropyl group has an analogy in the stabilization of a carbenium ion center by a cyclopropyl substituent. This interaction can also be recognized in the increased rate of solvolysis of certain cyclopropylmethyl compounds[18]: acceleration of the solvolysis and of the "nitrogenolysis" on cyclopropyl substitution should thus have similar origins. The formation of the end products can be easily explained by the interaction represented in *(8)*: charge transfer from the three-membered ring to the nitrene nitrogen weakens the bonds C^1—C^2 or C^1—C^3 in the cyclopropane and thus facilitates the rearrangement to the azetine or the cheletropic elimination of nitrile to give ethylene[21].

That the two last-mentioned compounds are not products of a subsequent thermal decomposition of the 1-azetine system can be demonstrated conclusively for pyrolysis of *(2)*: benzonitrile is formed at 102.5 °C in a first-order reaction with $k_1 = 2.91 \times 10^{-4}$ [s^{-1}], and this value is identical within experimental error with k_1 of the azide thermolysis.

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[1] This work was supported by the Deutsche Forschungsgemeinschaft.

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[6] Yields refer to the amine that reacted. Recoveries were 41% of the amine used for *(1)*, 20% for *(2)*, and 65% for *(3)*.

[7] The products obtained gave correct values on elemental analysis. IR, NMR, and mass spectra are in agreement with the structures proposed.

[8] This compound was recently prepared by a similar method by *D. S. Wulfman* and *T. R. Steinheimer*, Tetrahedron Lett. *1972*, 3933.

[9] The rate constants were determined by IR spectrophotometry with the asymmetric stretching vibration of the azide system as reference band.

[10] *G. Geiseler* and *W. König*, Z. Phys. Chem. (Leipzig) *227*, 81 (1964).

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[12] The main product of thermolysis of *(7)* is 2-phenyl-1-pyrroline.

[13] *R. B. Turner, P. Goebel, B. J. Mallon, W. v. E. Doering, J. F. Coburn*, and *M. Pomerantz*, J. Amer. Chem. Soc. *90*, 4315 (1968), and literature cited therein.

[14] *R. B. Woodward* and *R. Hoffmann*, Angew. Chem. *81*, 797 (1969); Angew. Chem. internat. Edit. *8*, 781 (1969).

[15] *A. D. Walsh*, Trans. Faraday Soc. *45*, 179 (1949); *R. Hoffmann*, Tetrahedron Lett. *1970*, 2907; *H. Günther, ibid. 1970*, 5173; *P. Bischof, R. Gleiter, E. Heilbronner, V. Hornung*, and *G. Schröder*, Helv. Chim. Acta *53*, 1645 (1970).

[16] It is not necessary to formulate free cyclopropylnitrene as an intermediate in the decomposition of the cyclopropyl azide. A strongly asynchronous process with extensive nitrogen-nitrogen bond cleavage in the transition state and late occurrence of the opening of the bond in the cyclopropane skeleton would profit from the same interaction *(8)*.

[17] *T. G. Taylor, W. Hanstein, H. J. Berwin, N. A. Clinton*, and *R. S. Brown*, J. Amer. Chem. Soc. *93*, 5715 (1971).

[18] *Z. Majerski* and *P. von R. Schleyer*, J. Amer. Chem. Soc. *93*, 665 (1971) and literature cited therein. The difference in the activation enthalpies for solvolysis of cyclobutylmethyl tosylate [19] and cyclopropylmethyl tosylate [20] amounts to 8 kcal/mol.

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[20] *D. D. Roberts*, J. Org. Chem. *29*, 294 (1964).

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A Direct Cyclobutene-Bicyclobutane Valence Isomerization[1][**]

By *Günther Maier* and *Manfred Schneider*[*]

Irradiation of tricycle *(1)* leads to fission into tetramethylcyclobutadiene and tetramethylpyridazine[2]. If it were possible to prepare the heterocycle *(2)* that is valence-isomeric with *(1)*, a substance would be available whose photofragmentation might open a route to tetramethyltetrahedrane.

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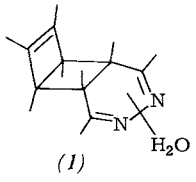
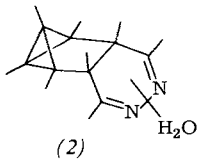
[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

We have now prepared the ozonide *(4)*, which appears to be an ideal starting material for the synthesis of *(2)*. Compound *(4)* [m.p. 142 °C; NMR (CCl_4): $\tau = 8.60$ (6H), 8.73

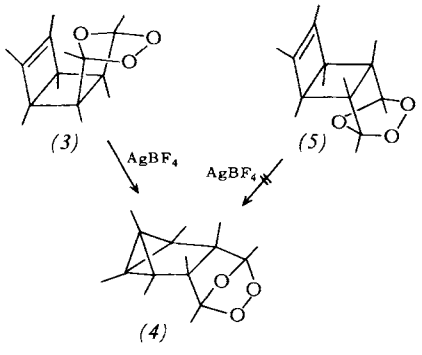


(1)



(2)

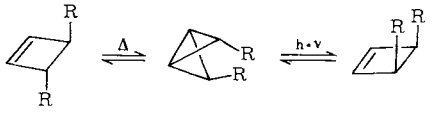
(3H), 8.77 (3H), 9.07 (6H), 9.20 (6H)] is formed surprisingly smoothly by the action of $AgBF_4$ on the valence-isomeric ozonide *(3)*[3]. Reducing *(4)* with triphenylphosphane affords the diacetyl compound, m.p. 179 °C, containing an intact bicyclobutane ring skeleton. Irradiation of *(4)* at room temperature or −70 °C effects fission into hexamethylbenzene and acetic anhydride.



(3) *(5)* *(4)*

It is noteworthy that the ozonide *(5)* having the *anti*-configuration is not rearranged under the same conditions. This is a result of the fact that the steric strain in the *syn*-isomer *(3)* is greater than that in *(5)*.

Valence isomerizations in the cyclobutene ⇌ bicyclobutane system are of interest in connection with the Woodward-Hoffmann selection rules[4]: the conversion of a cyclobutene of *cis*-configuration as in *(3)* into an *endo,endo*-disubstituted bicyclobutane such as *(4)* is thermally "forbidden", but it is "allowed" on photochemical excitation.



The rearrangement *(3)* → *(4)* described here is, to the best of our knowledge, the first example of the direct conversion of a cyclobutene into a bicyclobutane. At the same time it is a further confirmation[4, 5] that $Ag^{\oplus}$-ions can cause a reversal of the stereochemistry necessary for the thermal, non-catalyzed reaction.

9,10,11-Trioxapentacyclo[6.2.1.0^{2,7}.0^{3,5}.0^{4,6}]undecane (4)

Addition of 50 mg $AgBF_4$ to a solution of 5.00 g (0.019 mol) ozonide *(3)* in 40 ml dry acetone, stirring under nitrogen in a closed vessel for 16 h at 20 °C, evaporation of the solvent and filtration of the residue in petroleum ether through an Al_2O_3-column gives 4.50 g (90%) of bicyclobutane derivative *(4)*.

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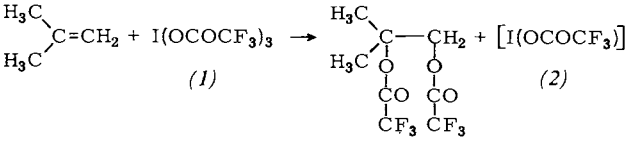
Stereospecific Oxidation of Alkenes by Iodine Tris(trifluoroacetate)

By *Joachim Buddrus*[*]

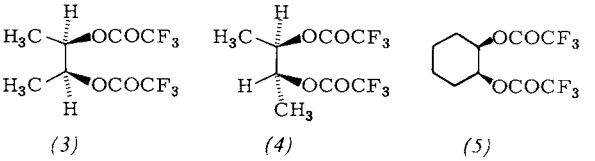
Acetates of metals in their higher oxidation states are known to act as oxidizing agents. For example, lead tetraacetate, thallium triacetate, and mercury diacetate convert alkenes into mixtures of the allylic acetates as well as the diacetates of *vic*- and *gem*-diols[1]. In such reactions the allylic acetate usually predominates. Insofar as they are formed at all, the ethylene acetates are diastereoisomeric mixtures.

It was observed that iodine tris(trifluoroacetate) *(1)*[2] also oxidizes alkenes. If it is suspended in olefin-free pentane and an alkene is then added dropwise at room temperature a rapid reaction occurs, esters of *vic*-diols being formed in yields of 50—70%. Isobutene affords 1,1-dimethylethylene bis(trifluoroacetate).



The iodine mono(trifluoroacetate) *(2)* formed simultaneously cannot be isolated, but only iodine; formation of *(2)* can, however, be demonstrated indirectly by adding an excess of alkene, which leads to the iodohydrins (as trifluoroacetate).

Oxidation of the alkene occurs largely stereospecifically. *cis*-2-Butene[3] gives mainly the *meso*-compound *(3)* [*(3)*:*(4)* = 97:3], *trans*-2-butene[3] gives mainly the *dl*-



compound *(4)* [*(3)*:*(4)* = 9:91]. Cyclohexene is converted into *(5)* and the corresponding *trans*-compound in the proportion 94:6. The isomers can be separated by gas

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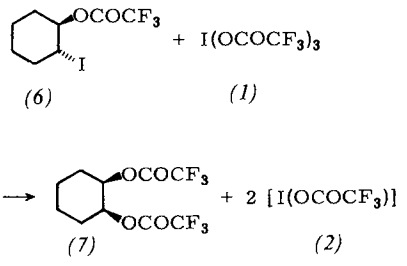
chromatography (stationary phase: 3,3'-oxydipropionitrile). They were identified by comparing their retention times and ^{1}H-NMR spectra with those of authentic samples[4].

The degree of stereospecificity depends on the polarity of the solvent. Thus the ratio between the amounts of the isomeric 1,2-diol derivatives from cyclohexene is 94:6 in pentane, 91:9 in chloroform and 85:15 in methylene dichloride. This dependence rules out a concerted mechanism[5]. A two-step mechanism may be presumed: electrophilic *trans*-addition of *(1)* to the alkene is followed by substitution of the carbon-iodine bond by the trifluoroacetate ion with inversion at the carbon atom. An inversion of this type can be demonstrated for the reaction of *(6)* with *(1)*, which also occurs in pentane at room temperature.



(6) *(1)* *(7)* *(2)*

In this reaction the *trans*-compound *(6)* [J_{CHI} = 10.5 + 9.5 + 4.5 Hz] passes into the *cis*-compound *(7)* [*(7)*:corresponding *trans*-compound = 95:5]. The mechanism is still under study.

The oxidation of alkenes by *(1)* can be compared with that of alkenes by iodine and silver salts of carboxylic acids in aqueous acetic acid as described by *Woodward* and *Brutcher*[6]. In both cases *cis*-1,2-diol derivatives are formed.

Orientation experiments show that rearrangements occasionally occur. Whereas isobutene and tetramethylethylene give only the expected derivatives of the *vic*-diols, 2-methyl-2-butene affords not only the *vic*-compounds but also 1,2-dimethylpropylidene bis(trifluoroacetate) which is a derivative of the *gem*-diol (ratio 2:1). Styrene is converted mainly into the rearranged product 2-phenylethylidene bis(trifluoroacetate).

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[1] For comparison of the oxidizing agents see *J. B. Lee* and *M. C. Price*, Tetrahedron *20*, 1017 (1964).

[2] *M. Schmeisser, K. Dahmen*, and *P. Sartori*, Chem. Ber. *100*, 1633 (1967).

[3] From Fluka, Buchs; purity ≥ 99%.

[4] *(3)* and *(4)* were prepared from the corresponding *meso*- and *d,l*-diols (from Bayer, Leverkusen) and trifluoroacetic anhydride.

[5] For the solvent-dependence of the stereospecificity of the bromination of stilbene see *G. Heublein*, Angew. Chem. *77*, 917 (1965); Angew. Chem. internat. Edit. *4*, 881 (1965); Z. Chem. *6*, 201 (1966); *8*, 108 (1968).

[6] *R. B. Woodward* and *F. V. Brutcher*, J. Amer. Chem. Soc. *80*, 209 (1958).

CONFERENCE REPORTS

Mechanism of Excitation of Photoreceptor Cells

By *Hennig Stieve*[*]

Photoreceptor cells function as interpreters that translate the light stimulus into the language of the nervous system. A receptor is an active biological transducer (amplifier).

Photoreceptor cells usually have a part containing an increased area of strongly folded surface membrane in which the photosensitive pigment, rhodopsin, is incorporated. A nerve fiber leads from the cell body carrying the excitation finally to other nerve cells. The stimulating light, which is absorbed by the photosensitive pigment, causes in the photoreceptor cells a series of reactions, which one refers to as excitation: absorption of a light quantum starts a photochemical reaction of the rhodopsin —namely, stereoisomerization of the chromophore 11-*cis*-retinal to all-*trans*-retinal—which is followed by a cascade of dark reactions. The dark reactions consist of changes in the protein portion of the rhodopsin. By some as yet not fully understood mechanism one of these reaction steps causes a transient change in the conductivity of the cell membrane and thus a transient change in the membrane potential of the photoreceptor cells. This voltage impulse, being the response to the light stimulus, is called the receptor potential.

The amplitude of the receptor potential amounts at most to 70 mV. It is larger the larger the intensity of the stimulating light. The change in conductivity of the photoreceptor cell membrane caused by the light stimulus is different in the visual cells of vertebrates from that in the photoreceptors of invertebrates. In invertebrates the conductivity at first increases on illumination, whereas in the visual cell membranes of the vertebrates it decreases transiently. The changes in the structure of the rhodopsin must be regarded as causing the opening or closing of pores in the visual cell membrane. This in turn causes changes in the ionic current through the cell membrane. Calcium ions play a decisive role in the process of opening and closing of the pores. It is assumed nowadays that a change in the calcium ion concentration due to a change in the conformation of the photosensitive pigment controls the conductivity of the visual cell membrane.

The voltage signal, called the receptor potential, spreads over the whole cell membrane and can set off a series of

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nerve impulses (spikes) in the membrane portions where the nerve fiber originates or at the synapses.

Lecture at Darmstadt on May 30, 1972 [VB 360 IE]
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Use of Deuterated Compounds in the Study of Tyrosine-Dopa Metabolism in Phenylketonuria

By *H.-Ch. Curtius*[*]

The use of radioactive isotopes for labeling of metabolic processes in man is not without risk and can be undertaken only in special cases. Non-radiating, stable isotopes such as ^{15}N, ^{13}C and deuterium have found little use so far because their measurement presented some analytical problems. The most suitable instrument for detection of stable isotopes is the mass spectrometer, but the separation and purification of the various compounds before mass spectrometry is very cumbersome and usually provides only low yields. Since the introduction of the combination of gas chromatography with mass spectrometry this problem has become much less serious. Complicated biological mixtures can now be separated by gas chromatography in amounts down to the nanogram scale and then analyzed for their isotope content in the mass spectrometer[1, 2].

We have studied the tyrosine and phenylalanine metabolism during phenylketonuria with the aid of stable isotopes. In this disease there is no conversion of phenylalanine into tyrosine, *i.e.* the phenylalanine-hydroxylase complex is defective. The causes of the symptoms of this disease (mental-retardation, neurological symptoms, partial lack of pigmentation) are still largely unknown.

Patients suffering from phenylketonuria with high plasma phenylalanine content excrete low concentrations of catecholamine metabolites in the urine. Investigations *in vitro* have shown that the conversion of tyrosine into dopa by tyrosine-hydroxylase isolated from bovine adrenal gland is inhibited by high phenylalanine concentrations[3]. To follow the conversion of tyrosine into biogenic amines in phenylketonuria patients *in vivo* we have carried out loading experiments with deuterated L-tyrosine (150 mg/kg body weight). The experiments were made with patients having high (25 to 35 mg/100 ml), moderate (15 to 20 mg/100 ml) and low plasma phenylalanine content (< 4 mg/100 ml) as well as with healthy controls. The excretion of tyrosine metabolites (dopamine, 4-hydroxy-3-methoxyphenylglycol, homovanillic acid, vanillylmandelic acid) in the urine was studied by gas chromatography linked to mass spectrometry. Patients with high phenylalanine plasma concentration showed only a very small increase in the above-mentioned metabolites, those with a medium phenylalanine concentration showed a somewhat greater increase. When the phenylalanine content was low we observed a large increase in the amounts of urinary metabolites, analogous to that in the healthy controls. These experiments show that the tyrosine-hydroxylase activity *in vivo* and thus the formation of biogenic amines and of L-dopa is dependent on the phenylalanine concentration in plasma and tissues. To confirm these results we loaded the same patients with 50 mg/kg body weight of L-dopa while their phenylalanine plasma level was high (about 30 mg/100 ml); the urinary metabolites in question were indeed excreted in appreciably higher concentrations after one administration of L-dopa.

The *in vivo* inhibition of L-dopa formation by phenylalanine could be an important factor in the pathogenesis of the neurological symptoms and the mental retardation of phenylketonuria patients.

Lecture at Konstanz, July 6, 1972 [VB 358 IE]
German version: Angew. Chem. *85*, 176 (1973)

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[1] *J. L. Pinkus, D. Charles*, and *S. C. Chattoraj*, J. Biol. Chem. *246*, 633 (1971).
[2] *H.-Ch. Curtius, J. A. Völlmin*, and *K. Baerlocher*, Clin. Chim. Acta *37*, 277 (1972).
[3] *M. Ikeda, M. Levitt*, and *S. Udenfriend*, Arch. Biochem. Biophys. *120*, 420 (1967).

ABSTRACTS

The lipids of mycobacteria, which are reviewed by *M. B. Goren*, play an important role for the relationship between these bacteria and the host organisms. The structural variety of the substance class became apparent only with the aid of modern analytical methods. It has not yet been established whether the compounds which are mainly isolated from *in vitro* cultures are not artifacts since the chemical structure of the bacteria depend upon their environment. In the cell the substances are probably in a defined arrangement; it was shown for the phosphatides that their immunological activity is greatly enhanced by complex formation. Some representatives of the high-molecular weight waxes D, chloroform-soluble peptidoglycolipids of the cell wall, could serve as starting materials for the eludication of the relationship between chemical structure and physiological activity of the substances by a synthetic method. [Mycobacterial Lipids: Selected Topics. Bacteriol Rev. *36*, 33—64 (1972); 268 references]

[Rd 546 IE—R]

The surface properties of calcium phosphates represents the theme of a summarizing report by *C. L. Kibby* and *W. K. Hall*. Calcium phosphates having an apatite struc-

ture, primarily hydroxyapatite, are the main components of bones and teeth. The crystals are exceptionally small and the surface area correspondingly large, *e.g.* 1 to 10 m^2/g for tooth enamel and 60 to 100 m^2/g for bone mineral. The apatite structure permits numerous ionic substitutions and defects and the number of possible modifications is so great that it is often difficult to decide whether an experimental result applies only to the sample in question or whether it is of more general validity. Changes in chemical composition naturally produce changes in surface properties. [Surface Properties of Calcium Phosphates. Chem. Biosurfaces *2*, 663—729 (1972); 183 references]

[Rd 552 IE—G]

Measurements of adsorption at electrodes are critically discussed by *H. H. Bauer*, *P. J. Herman*, and *P. J. Elving*. The authors consider the question: How can adsorption at electrodes be measured, and what information can be gained from the results? Adsorption at electrodes differs from other adsorption processes in that the electrical potential of the adsorbent can be varied independently. Furthermore, electron transfer reactions whose occurrence is potential-dependent can be superimposed on the adsorption process. [Critical Observations on Measurements of Adsorption at Electrodes. Mod. Aspects Electrochem. *7*, 143—197 (1972); 305 references]

[Rd 554 IE—G]

Transport-controlled deposition and dissolution of metals is the title of a review by *A. R. Despić* and *K. I. Popov*. Structure and appearance and the nature of the surface of a deposited metal are largely dependent upon the pathway and the rate of flow of the deposited species. Rate-determining transport processes therefore play a role in the formation of irregularities, in formation of dendrites, whiskers, and powdery deposits, as well as in the processes employed in the removal of these irregularities (electropolishing, *etc.*). The article surveys the current state of the art and the uniform theoretical treatment of the processes mentioned. [Transport-Controlled Deposition and Dissolution of Metals. Mod. Aspects Electrochem. *7*, 199—313 (1972); 131 references]

[Rd 555 IE—G]

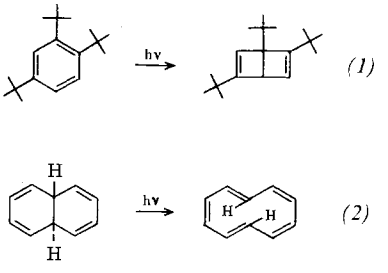
The application of ESR spectroscopy to problems of catalyst research is reviewed by *J. H. Lunsford*. The information available from ESR data ranges from the confirmation of the presence of an unknown paramagnetic species to the detailed description of bonding and orientation of a surface complex. The high sensitivity of the method makes it of particular interest in catalyst research since it permits the study of very low concentrations of active sites. Thus unexpected valence states and intermediates (for instance the anions O_2^- and O^-) have been be detected by ESR spectroscopy. [Electron Spin Resonance in Catalysis. Advan. Catal. *22*, 265—344 (1972); 174 references]

[Rd 574 IE—G]

Heat-flow microcalorimetry and its application to problems of heterogeneous catalysis is the topic of a review by *P. C. Gravelle*. Principle of the method: the inner vessel of a calorimeter is connected to its environment by a thermal conductor. If heat is evolved or consumed, a flow of heat is set up until thermal equilibrium is reestablished. The temperature difference between the two ends of the thermal conductor is measured as a function of time. The article considers: types of calorimeters; theory of the measuring technique; evaluation of the experimental results; and applications to problems of heterogeneous catalysis. It becomes apparent that heat flow calorimetry is subject to fewer theoretical and practical limitations than other calorimetric techniques. It is therefore particularly suitable for studies on surface processes on solids of poor thermal conductivity, which includes most industrial catalysts. [Heat-Flow Microcalorimetry and Its Application to Heterogeneous Catalysis. Advan. Catal. *22*, 191—263 (1972); 84 references]

[Rd 575 IE—G]

Valence bond isomers of aromatic and heteroaromatic systems are the subject of a review by *E. E. van Tamelen*. Since the synthesis of the Dewar-benzene derivative *(1)* a decade ago many other such valence bond isomers have been detected, such as the highly unstable cyclodecapentaene ([10]annulene) *(2)* that is formed from *trans*-9,10-dihydronaphthalene. In contrast, the 1,6-bridged [10]annulenes are stable. Numerous other examples, *e.g.* bullvalene, are to be found among the $(CH)_{10}$ hydrocarbons.



The author also discusses, *inter alia*, valence bond isomeric systems characterized by participation of ions and heteroaromatic compounds. [Valence Bond Isomers of Aromatic Systems. Accounts Chem. Res. *5*, 186—192 (1972); 62 references]

[Rd 579 IE—L]

Radical anions and carbanions as donors in electron-transfer processes is the title of a report by *M. Szwarc*. Rates and free energies of the reactions depend upon the form of the participating ions (free ions, ion pairs, higher aggregates). Systems with two or more ionic species are particularly interesting. Thus biphenyl anion ($Biph^{\cdot -}$) and naphthalene (Naph) equilibrate with biphenyl and naphthalene anion:

$$Biph^{\cdot -}, Na^+ + Naph \rightleftharpoons Biph + Naph^{\cdot -}, Na^+$$

Carbanions can transfer an electron to aromatic acceptors (A), *e.g.*:

$$Ph_3C^- + A \rightarrow Ph_3C^{\cdot} + A^{\cdot -}$$

The author also considers reactions of dianions and ionic aggregates and the methods of studying these reactions.

[Radical Anions and Carbanions as Donors in Electron-Transfer Processes. Accounts Chem. Res. 5, 169—176 (1972); 43 references]

[Rd 580 IE—L]

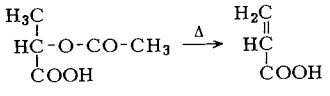
Patents

Abstracts of selected "Deutsche Offenlegungsschriften" (DOS), *i.e.* provisionally published specifications as filed with the German Patent Office

***trans*-Polyalkenamers having a broad molecular weight distribution** are prepared by polymerization of cycloolefins with ring cleavage in inert organic solvents with organometallic mixed catalysts consisting of tungsten compounds, organoaluminum compounds, and possibly catalysts. The polymerization is carried out in the presence of hydrogen chloride, the molar ratio of hydrogen chloride to the tungsten compound being 0.1 : 1 to 10 : 1. The broad molecular weight distribution of the polymers is reflected in the values for the Defo hardness and elasticity. The material exhibits excellent sheet formation on the mill. Because of the good shear gradient excellent dispersion of fillers and additives occurs during processing on the mill or in the internal mixers. The polymers, which exhibit excellent vulcanization properties even in highly filled and oil-extended mixes, are used as synthetic rubber. [DOS 2056178; Farbenfabriken Bayer AG, Leverkusen]

[PR 45 IE—E]

In a new synthesis of acrylic acid, α-acetoxypropionic acid *(1)* is passed at 200—500 °C over catalysts containing phosphates of metals of group I and/or II of the periodic system, possibly on support materials such as silica, Al_2O_3, silicates, pumice stone, and charcoal. In the past, acrylic



(1)

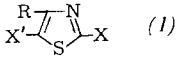
acid was obtained, *e.g.* by thermolysis of β-hydroxypropionic or β-acetoxypropionic acid, which are difficult to obtain. In the thermal cleavage of the free acid under the conditions of the cleavage of α-acetoxypropionic acid derivatives, acetaldehyde and carbon monoxide are formed. [DOS 2046411; Farbwerke Hoechst, Frankfurt/Main-Höchst]

[PR 48 IE—B]

Novel alcohol-promoted chromium oxide-aluminum oxide catalysts for the production of aromatic hydrocarbons, particularly of *p*-xylene, by dehydrocyclization of diisobutylene or triisobutylene and/or their hydrogenation products are claimed. The catalysts have the following composition: 10 to 25% of Cr_2O_3, 1 to 5% of K_2O, 0.5 to 4% of SiO_2, 67 to 88.5% of α-Al_2O_3. A special advantage claimed for this process is the low carbon formation. [DOS 2144226; Deutsche Akademie der Wissenschaften, Berlin]

[PR 51 IE—D]

Thiazoles *(1)* can be used as condiments and flavors, particularly for foods and allied products as well as for perfumed products. Other flavoring substances, supports, stabilizers,



(1)

R = H, acyl, alkyl; X = H, alkyl, alkoxy; X' = H, alkyl, acyl, alkoxy

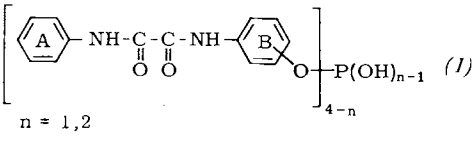
thickening agents, surface active agents, conditioners, and taste-increasing agents may be added to them. [DOS 2152557; International Flavors & Fragrances Inc., New York]

[PR 52 IE—D]

The sound absorption of soundproofing layers for motor vehicles based on castable polyester or polyether urethane foams is substantially improved by addition of a mixture of 200—400 parts by weight of barite (based on the polyol component) with 10—30 parts by weight (based on the barite) of alkanesulfonic ester, *e.g.* of phenol or cresol. The addition of this latter substance, which is itself known, and which has plasticizing properties, leads to a surprising decrease in the viscosity of the final reaction mixture. It is thus possible to obtain a large increase in the density, which is directly responsible for the effectiveness of thermal and particularly acoustic insulation. The barite may be entirely or partly replaced by other heavy fillers, and the alkanesulfonic ester may be entirely or partly replaced by other plasticizers. [DOS 2063588; Phoenix Gummiwerke AG, Hamburg]

[PR 59 IE—O]

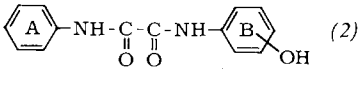
New organic phosphorus compounds having the general formula *(1)* stabilize organic materials, in most cases simultaneously against the destructive action of UV light, visible light, air, and heat. This broad action spectrum makes them particularly valuable as stabilizers for plastics, *e.g.* polypropylene, to which they are added before processing. The benzene ring A may be substituted by alkyl,



(1)

n = 1,2

alkoxy, or hydroxyl groups; the benzene ring B may contain a methyl group. The compounds *(1)* are prepared by reaction of $4-n$ moles of a diaryloxamide *(2)* with one mole of phosphorus trichloride or tribromide; when $n = 2$, a reaction with one mole of water follows. [DOS 2150787; Sandoz AG, Basel]



(2)

[PR 74 IE—U]

Inorganic Vibrational Spectroscopy. Vol. I. By *L. H. Jones*. Marcel Dekker, Inc., New York 1971. 1st Edit., viii, 218 pp., numerous tables, bound, $ 22.50.

The contents of the present book are much narrower in scope than its title would lead one to suppose. It is restricted to an evaluation of the fundamental vibrations of those inorganic molecules and complex anions for which experimental work allows a complete calculation of the force constants. Besides diatomic and triatomic molecules, the author deals with some halides of the type XHal , as well as with mononuclear cyano and carbonyl complexes of higher symmetry, calling upon his own contributions to the spectra and force constants of these compounds. Additional parameters such as isotope frequency shifts and Coriolis force effects are taken into account in determining force constants. The possibilities of correcting for anharmonicity and its effect on the calculated force constants are demonstrated. As a rule, the author bases the force constants on the general force field, but in some cases he also uses a modified Urey-Bradley field. Some statements are made on the interpretation of force constants, especially interaction constants, although no generally applicable conclusions can be drawn at the present time.

The introduction to the special section takes the form of a brief outline of the theory of molecular vibrations, with discussions of the energy relationships for harmonic and anharmonic vibrations, G and F matrices, internal coordinates, symmetry coordinates, redundance relationships, and potential fields. This part of the book, in conjunction with the examples and tables given in the appendix, can help the advanced student to get the hang of normal coordinate calculations. On the whole, however, the restricted scope of the book makes it more likely to be useful for those working in vibrational spectroscopy for the derivation of special results and for the literature references.

H. J. Becher [NB 100 IE]

Techniques of Chemistry. Vol. I: Physical Methods of Chemistry. Edited by *A. Weissberger* and *B. M. Rossiter*. John Wiley & Sons, Inc., New York—London 1971. 1st Edit., Part I A: xi, 433 pp., numerous figures, bound £ 9.50. Part I B: xi, 330 pp., numerous figures, bound £ 8.00.

After several editions, the series "Techniques of Organic Chemistry" edited by *A. Weissberger* now appears under the title "Techniques of Chemistry". The first volume deals in five parts with the physical methods commonly used in chemistry. Parts I A and I B have now been published.

Part IA deals with the basic mechanical, electrical, and electronic components of scientific instruments. The section "Mechanical" presents the possibility of producing mechanical movements, the types of motors, and the physical layout of such systems. In the sections "Basic Electrical Principles" and "Electronic Components", the electrical and electronic components of instruments and their theoretical principles (measurement of resistances and capacities, circuits, amplifiers, current supply equipment, AD and DA converters, semiconductor electronics, *etc.*) are discussed. The nature and reproduction of electrical signals, the difference between analog and digital signals, and "digital logic" are also discussed. The last section of this volume is devoted to the production and modulation of electromagnetic waves, optical sources, and the production of acoustic signals.

The first section of Part I B presents a survey of detectors for radio waves and microwaves, for the optical range (IR, UV/visible), and for radioactive radiation, while the principles of automatic systems are described in the next two sections. The last section deals with the mathematical basis, the construction, and the functioning of analog and digital computers, as well as possibilities for their use in chemistry.

The two volumes are well illustrated. The various sections, which are written by different authors, end with very useful references to reviews and other important literature. The subject index could have been more detailed. The books appear at a time when instrumental methods are being increasingly used in all branches of chemistry. Their value cannot therefore be overestimated. To whom can they be recommended? To any chemist (or even biologist) whose electrical and electronic instruments are more to him than the infamous black box. In these volumes he can learn what was omitted from the practical physics course in many universities, and still is omitted in part; he can also learn about the functioning of a pen recorder, a photomultiplier, a semiconductor component, *etc.* He will find what he is looking for condensed to the essentials as far as he is concerned, and presented in a form that he can understand. He can also learn about the fundamentals of electronic data processing. For example, he will learn in a few lines the meaning of the 5-channel BCD code in which he punches the values for his HMO and kinetic calculations. The two volumes occupy a unique position in present-day support literature for chemists and biologists.

Egon Fahr [NB 97 IE]

Partition of Cell Particles and Macromolecules. By *P. Albertson*. Almqvist & Wiksell, Stockholm 1972. 2nd Edit., 323 pp., numerous figures, bound Sw.kr. 72.25.

The development of chemistry started with methods for the separation of low molecular weight substances; the refinement of these methods and their application to the complicated mixtures of cell components and metabolites characterized the progress of biochemistry to the stage of our present knowledge of macromolecules. The purification of enzymes, nucleic acids, and many complex cell components is now routine in the laboratory, and is even carried out semi-industrially in some cases. On the other hand, investigations on labile cell particles, viruses, and cells as well as on other multicomponent mixtures of biological colloids are still hindered by purification problems, particularly where fairly large quantities are concerned. Apart from modern centrifugation methods and separations on molecular sieve columns, partition chromatography in aqueous multiphase systems, which was developed by *Albertson*, has recently been making a name for itself.

The second edition of the present monograph is a thorough modernization and revision of the book that appeared ten years ago, with the incorporation of the more recent findings. This clearly written and skillfully arranged book begins with the Brønsted equation for partition in two-phase systems and deals with this theory from various

angles, but always in an understandable manner and with an eye to practical applications, which are illustrated by numerous examples of the fractionation of cells, mitochondria, chloroplasts, viruses, and protein/protein and nucleic acid/protein complexes. Single partitions are suitable for mixtures of macromolecules with very different molecular parameters. Others must be separated by multi-stage countercurrent partition, for which *Albertson* has designed an effective apparatus. The method is thus suitable not only for the separation of particles but also for the study of bonding between particles or molecules. The many examples and the carefully evaluated literature make this seem an attractive method for a number of outstanding problems, though patience and experience are evidently necessary for successful results. However, the beginner is given access to the theory and application through numerous tables and data on the behavior of aqueous polymer/polymer phases. The book will thus be welcomed by chemists and biologists who are concerned with the separation and the biochemical and physical behavior of cell organelles, and also as a practical guide.

L Jaenicke [NB 101 IE]

Methoden der Organischen Chemie (Methods of Organic Chemistry) (Houben-Weyl). Edited by *E. Müller*. Vol. IV/Part 4: Isocyclic Four-Membered Ring Compounds, by *D. Seebach*. Appendix: Cyclopropane and Cyclobutane Derivatives from Natural Products, by *S. Beckmann* and *H. Geiger*. Georg Thieme Verlag, Stuttgart 1971. 4th Edith., xxviii, 568 pp 47 tables, bound DM 258 —

The volume is a very comprehensive summary of the physical and chemical properties of isocyclic four-membered ring compounds. The material in the main part (444 pages) is divided into chapters on the preparation and the reactions of four-membered ring derivatives, an arrangement that has proved satisfactory in the past. The classification is mechanistically oriented, and contains ordering principles of modern structural theory. Wherever possible the author succeeds in explaining stereochemical findings in the language of orbital symmetry control without lengthy theoretical descriptions. This becomes his dominant theme with the result that the reader is not only required to note modes of reaction, but his understanding is also challenged.

The volume ends (29 pages) with an enumeration of natural products having cyclopropane and cyclobutane structural units and data on their occurrence and their structure. More detailed information on any syntheses of these substances would have been of great value to the chemist (*e.g.* information on the elegant syntheses of the bourbonenes is lacking on p. 470).

The preparation of four-membered rings is guided by formal patterns of atoms linked (p. 30), which bring some lucidity and order to the many reactions used. However, the price of excessively strict adherence to this principle is that mechanistically related or identical reactions (*e.g.* Chap. Ia, pp. 31—53 and Chap. II, pp. 119—125), which belong together, appear in different parts of the book. To help the reader to overcome this obstacle, the author consistently provides cross references, of which there are too many rather than too few.

On the whole, the main part has been presented painstakingly and well by the author and by the publishers. The expert selection of the numerous synthesis procedures and the physical data that are given for practically all the compounds mentioned ensure optimum information for the user, and the numerous references to recent literature that are incorporated into the footnotes give the volume an up-to-dateness that is sometimes lacking in the other volumes of the series because of long publication times.

The volume ends with an author index, a subject index, and an index of synthesis procedures. A new feature of the subject index is the inclusion of basic structural types of classes of compounds before the appropriate columns, so that the reader in a hurry can find the desired class of compounds simply by inspection of these basic structures. Substituents are then arranged according to the Beilstein system.

The disadvantage of this arrangement in classes of substances is that it is difficult to find a reaction type from the index. For example, the "metathesis of olefins", which is dealt with on p. 299, cannot be found from the index. Some of the treasures of the book can thus be found out only by intensive reading.

A few points that occurred to the reviewer may also be mentioned in conclusion.

The text contains very few printing errors. The presentation of the reaction mechanism with formulas on p. 305 strikes the reviewer as unnecessary, since the structure of the reaction product has not yet been verified. The preparation of the compound IIIb (pp. 242—243) requires the use of 3,4-*cis*-dichlorotetramethylcyclobutene, whose preparation should be described on p. 307. However, the preparation of the *trans* compound is described on this page. The addition of dichlorovinylene carbonate to acetylene is not described on pages 239 and 242, as it should be according to page 341. The cyclobutenediylium dyes deserve more then a mention in footnotes. The perfluoro derivatives enumerated on p. 214 do not include tetrafluorocyclobutane-1,2-dione, which has surprising properties.

Nevertheless, the book is unquestionably a very valuable addition to the Houben-Weyl series[1]. It provides the synthetic chemist with a fund of information on methods, and the theoretical chemist with a number of starting points. For example, the commonly used term "activated double bond" is defined differently on pages 185, 188, 216, and 267, and certainly could not be understood without the particular reactants; this is a wide field for those intersted in perturbation theory.

H.-D. Scharf [NB 102 IE]

[1] Cf. Angew. Chem. internat. Edit. *10*, 433 (1971).

Advanced Organic Synthesis, Methods and Techniques. By *R. S. Monson*. Academic Press, New York—London 1971. 1st Edit., xii, 230 pp., numerous figures, bound $ 7.95.

The foreword to this book announces a collection of modern reactions that have won a place in synthetic organic chemistry. The book is addressed to advanced students and postgraduate workers. It is evidently an attempt to make the important reactions, which are widely scattered in the original literature and in reviews, directly accessible with detailed experimental procedures. This would have been very useful if it had been correctly executed, since it might have helped to overcome the well-known barrier to the use of a new reaction that has not become established in the particular research group. However, the

stated objective has been satisfactorily achieved only in a few chapters. Chapters 4 (Hydroboration), 9 (Enamines), 11 (Wittig Reaction), and 12 (Reactions with Trialkylboranes) do in fact provide good, representative procedures that should be easy to apply to a range of compounds.

In the other chapters the selection is very arbitrary and not so good as it might have been. The inclusion of reactions as old as a chromic acid oxidation and the epoxidation of cyclohexene under oxidations, while the many variations of solvolytic oxidation with dimethyl sulfoxide are not mentioned, the failure to mention hydride complexes such as tri-*tert*-butoxy hydridoaluminate under hydride reductions, and the inclusion of a triviality like the ketalization of cyclohexanone in Chapter 7 (Elimination, Substitution, Addition) while many modern addition reaction, such as the regioselective and stereoselective addition of iodine azide, which leads to interesting intermediate products, are not mentioned are only three very obvious instances. Others could be added to the list.

Even the procedures selected do not always meet with approval. When *e.g.* the Wolff-Kishner reduction is described on p. 55 in its oldest form (ethylene glycol/KOH; 200 °C) while the much more active system potassium *tert*-butoxide/dimethyl sulfoxide, which has been known for some time, is not even mentioned, the stated aim has clearly not been achieved.

Finally, the reader gains the impression that organic chemistry is the chemistry of alicyclic compounds, as other fields are scarcely touched upon; however, it is a well-known fact that heterocyclic compounds are frequently rather neglected in American books. Verdict: Recommended with some hesitation.

Ekkehard Winterfeldt [NB 104 IE]

Pesticides in the Environment. Vol. 1, Part. 1. Edited by *R. Withe-Stevens*. Marcel Dekker, Inc., New York 1971. 1st Edit., xv, 270 pp., numerous figures and tables, bound $ 23.50.

According to the foreword, the editor's intention in the planned five-volume compendium is to present a comprehensive survey of the chemical, biological, and toxicological properties of the pesticides in current use, as well as their practical use and their behavior in the environment. Experts both from universities and from industry have contributed as authors of the various sections. Volume 1 (two parts) will deal with mainly scientific aspects, while Volume 2 (three parts) will be concerned with the use of the pesticides.

The present volume is divided into three chapters. In Chapter 1 "Chemistry and Biology of Pesticides" (*R. L. Metcalf*), some 600 chemicals are mentioned on 140 pages under the headings fungicides, herbicides, insecticides, molluscicides, nematocides, and rodenticides. The chemistry, structure-activity relations, mode of action, action spectrum, and toxicology are described for each group of substances. 165 references are cited, the latest being from the year 1966. This should be quite useful as a basis for the following sections, but seen in isolation it has a number of shortcomings in comparison with similar, more recent publications, most of which are more comprehensive. Thus, despite the terse form, no distinction is made between the preparations that are widely used at present and those that are only of historical interest or that never progressed beyond the development stage. The description does not correspond to the current position. It contains none of the modern fungicides against mildew and rice diseases and none of the systemic fungicides; the preparations of the amidine and triorganotin types, which are important at present in resistant areas, are not mentioned among the acaricides; and herbicides *e.g.* of the nitrodiethyl ether type are not discussed.

The second chapter "Metabolism of Insecticides and Fungicides" (*T. R. Fukuto* and *J. S. Sims*) comprises 90 pages with 344 references. Apart from the fact that the latest article cited dates from 1967, this is probably the most comprehensive account in existence of the degradation reactions of insecticides in cultivated plants, domestic animals, soil, and water, which are extremely important to the assessment of the nature and duration of their biological effects, toxication and detoxication processes, and toxicological dangers, as well as to residue analysis. The discrepancy in the description of the metabolism of insecticides (phosphorus compounds 40 pages, carbamates 12, chloro-organic insecticides 15) and that of fungicides (5 pages), which is practically limited to preparations of the thiocarbamate and captan types, is no fault of the authors, but reflects the serious gaps in the investigations.

Chapter 3 "Metabolism of Herbicides" (*J. E. Loeffler* and *J. van Overbeek*), which occupies 34 pages and includes 146 references, is unquestionably the most up-to-date section (several references from 1969). Unlike Chapter 2, it is arranged not according to chemical principles but on a broader basis. An introduction to the general principles, problems, methods, and techniques of metabolic studies (8 pages) is followed by separate discussions of the degradation reactions: photochemical transformations, nonenzymatic reactions, oxidation, conjugation, hydrolysis, and others. The metabolic principles found in nature are thus presented in a very understandable manner.

The book will be a very useful orientation aid even to the expert, not the least of its merits being the numerous references.

Klaus Sasse [NB 106 IE]

Die Prüfung thermoplastischer Kunststoffe (Testing of Synthetic Thermoplastics). By *H. J. Orthmann* and *H. J. Mair*. Carl Hanser Verlag, München 1971. 1st Edit., 163 pp., 50 figures, 43 tables, bound DM 28.—.

The methods and conditions for the testing of synthetic thermoplastics are largely described and specified in standards. The terse, dry language of standards, which arises mainly from the need to define all the conditions for a given test method as briefly as possible and with no possibility of mistake, makes the standards difficult to use as instructions for the execution of a test.

The present book fills a need in this respect. The principle of the test methods is described with reference to the corresponding standards, emphasis being placed on information that is not usually found in standards but is part of the experience of the plastics tester, such as data on the accuracy of the methods and on possible sources of error, relationships with similar methods, and the practical significance of the test results. Useful features are the list of bodies and associations that issue standards, recommendations, and quality guides, and particularly the guidance on the evaluation and statistical analysis of test results.

The book is thus a good introduction to techniques for testing synthetic thermoplastics, which offers guidance to those who wish to take up the testing of plastics, and provides those concerned with the buying and selling, processing, and use of plastics, to whom these substances are

presented with test data, with the knowledge required to interpret these data correctly.

Werner Waldenrath [NB 107 IE]

Einführung in die Immunchemie und Immunologie (Introduction to Immunochemistry and Immunology). Heidelberger Taschenbücher Vol. 79. By *E. A. Kabat*. Springer-Verlag, Berlin–Heidelberg–New York 1971. 1st Edit., viii, 322 pp., 107 figures stitched DM 18.80.

The present volume is a translation, undertaken by members of the Max-Planck-Institut für Immunbiologie in Freiburg, of the American original published in 1968. Despite the fact that recent developments in the domain of immunology have been left out of the account (literature references up to 1967), this book provides a splendid "introduction to immunochemistry and immunology." The theoretical principles of immunochemistry and immunobiology are clearly set forth in a series of well thought-out chapters, followed by a detailed description, with illustrations, of the relevant methods. The most important techniques for the detection of antigens and antibodies are described so lucidly as to enable the reader to apply them in practice without further ado.

The book is suitable not only for students, but also for physicians, biochemists, and chemists whose work requires them to use immunological techniques or confronts them with problems in the area of immunology. A detailed subject index is provided.

Gerhard Schwick [NB 110 IE]

Inorganic Reaction Mechanisms. Vol. I. Specialist Periodical Reports. Published by The Chemical Society London 1971. 1st Edit., xv, 338 pp., bound, £ 7 —

One of the innovations in the program of the Chemical Society is the series of "Specialist Periodical Reports". These volumes, which are very similar in presentation and style to the well-known "Annual Reports", are to be published at regular intervals of one to two years, and are intended to present substantially complete literature surveys of the special field of chemistry covered.

The present book covers the literature that became available to the authors between January 1969 and August 1970 on kinetics and mechanisms of inorganic reactions in solution. Including the reviews mentioned, *J. Burgess* ("Senior Reporter"), *D. N. Hague*, *R. D. W. Kemmitt*, and *A. McAuley* have evaluated more than 1700 publications. The book, which contains numerous tables and an author index, is very logically arranged and subdivided by mechanistic aspects and by substance, so that a subject index is unnecessary.

The volume contains four main parts:
1. Electron Transfer Processes; 2. Substitutions and Related Reactions; 3. Complex Formation with Labile Metals and Biochemically Interesting Reactions; 4. Organometallic Compounds (only transition metals and mercury).

At the abstractor's discretion, publications are discussed in detail or merely mentioned. The main parts and the subchapters are mostly preceded by short introductions, in which the scope of the subject matter is defined and any reviews are mentioned.

The task of presenting a succinct but readable account of a very large number of articles naturally has its problems; in the reviewer's opinion, some publications have received too much or too little attention, and the emphasis sometimes appears to have been wrongly placed in rendering the content of a report. Nevertheless, for those who are actively engaged in research, the book will prove to be of valuable assistance in overcoming the tiresome literature problems if it is accepted that the reports cannot appear until nine to twelve months after the publication of the latest articles reviewed. Those interested who are not experts in this field will find here a means of gaining a quick and reasonable insight into a relatively young field that still has many problems to be solved.

Jörn Müller [NB 105 IE]

Fluorocarbon and Related Chemistry. Vol. 1. Specialist Periodical Reports. Published by The Chemical Society, London 1971. 1st Edit., viii, 307 pp., numerous illustrations, bound £ 7 —

The present first volume of the series represents a review of the literature covering the years 1969 and 1970. It is proposed to cover the entire chemistry of highly fluorinated organic and organometallic compounds in a two-year cycle.

R. E. Banks and *M. G. Barlow*, both of whom enjoy an international reputation in the field of organic chemistry of fluorine, provide a detailed survey of work on organofluorine compounds, so that the book fully lives up to the title of the series.

This book, which is written in a clear and sober style, represents far more than the usual literature survey. In dividing the 300 pages into five chapters, the authors have hit upon a simple arrangement, but one that may well be just what is wanted for a field with so many ramifications as fluorine chemistry. Chapters 1 and 2 cover saturated fluorinated hydrocarbons and per- and polyfluorinated olefins and acetylenes. The chemistry of the carbonyl group forms the subject of Chapter 3. Chapter 4 deals with all the remaining organoelemental compounds, following the order of the Periodic Table. This somewhat unusual arrangement may admittedly make a given compound more difficult to find for an organic chemist thinking in terms of functional groups; nevertheless, it proves to be an advantageous one, especially in view of the large number of papers on organometallic compounds. The chemistry of per- and polyfluorinated aromatic compounds is sensibly given in a separate chapter. The last section of some 25 pages contains the most recent results in ^{19}F-NMR spectroscopy.

The printing and the presentation of the book are of a high standard. Numerous formulas and reaction schemes are given, together with the mechanisms and brief details of preparation. Indeed, in this form the book encourages one to leaf through and read it. An additional reference list at the end of each chapter supplements literature citations appearing on each page. The book closes with an appendix containing details of important publications, standard works in the field of fluorine chemistry, and a list of authors. There is unfortunately no index, so that in trying to solve certain problems the reader may involve himself in an intensive search.

The commendable speed with which it has been published preserves the book's topicality, and its aims make it an excellent complement to the other periodicals appearing in the field of fluorine chemistry. One of the volume's outstanding features is its presentation, which manages to avoid giving the impression of a textbook whilst retaining clarity and cohesion.

G. Büttner [NB 111 IE]

Preparative Acetylenic Chemistry by *L. Brandsma*. Elsevier Publishing Co., Amsterdam—London—New York 1971. 1st Edit., x, 207 pp., 14 figs, 3 tables, bound £ 8.20.

In a foreword written by his famous teacher, Prof. *Arens*, the author is praised for the care with which the book is written and for the usefulness of this collection of recipes, which are arranged in nine chapters as follows: 1. General practical information: 2. Preparation of metal acetylides; 3. Alkylations at the acetylene carbon and related reactions; 4. α-Hydroxyalkylation, -carboxylation, and -acylation at the acetylene carbon; 5. Direct introduction of hetero-substituents; 6. Preparation of acetylene compounds by means of elimination reactions; 7. Base-induced migration of the triple bond; 8. Various syntheses; 9. Starting compounds. Further information regarding the contents will be found in a type index and in an index of empirical and structural formulas, extending over some eight pages.

According to the author, this collection of recipes is not intended merely for the specialist in the field; however, one must mention in this context a very serious drawback, namely that, incredibly enough, the book contains practically no literature references! By way of justification it is explained in the introduction that the principles of *Raphael, Rutledge, Viehe*, and *Ziegenbein* have been adequately dealt with. There are thus practically no simple comparisons with the original literature. However, if the critical user takes the trouble to look up original works, he will often find himself wondering why changes have been made without comment or reference. Without this deplorable shortcoming this otherwise useful book would have been even more recommendable.

Heinz Günter Viehe [NB 108 IE]

Synthetic Methods of Organic Chemistry. Vol. 25. By *W. Theilheimer*. S. Karger Verlag, Basel 1971. 1st Edit., xvi, 707 pp., bound DM 296.—

"Theilheimer", which has been appearing annually for 25 years and which has now notched up 22357 selected abstracts covering all areas of preparative organic chemistry, constitutes an invaluable aid to anyone carrying out syntheses. The present volume contains abstracts of 700 original papers published during the period 1968—1970. This volume contains in addition the citations from volumes 21—24 in the text and in a comprehensive general index (161 pages), which covers methods, compound classes, and reagents. This makes the book much easier to use, especially for those readers for whom the Weygand system on which the arrangement is based represents a serious "energy barrier"!

As in the past, the seven-page section on "Trends in Synthetic Organic Chemistry", which contains a brief description of synthesis methods and information of general interest from the latest literature, is especially readable. The use of India paper has made it possible to keep the size of the current volume, which contains more information than ever before, within reasonable limits. Apart from two missing pages (550 and 551) in the reviewer's copy and some absence of care in the drawing of a few steric formulas, the printing and presentation are up to the usual excellent standard.

In view of the plethora of abstract literature available to the organic chemist at the present time, one might be tempted to question whether "Theilheimer's" continued existence is still justified. In the reviewer's opinion no other work can compare in the speed, detail, or clarity with which "Theilheimer" abstracts the literature on synthetic methods. It is therefore most desirable that students of chemistry should become acquainted with the Weygand system at the earliest possible stage.

Lutz-F. Tietze [NB 109 IE]

Organic Fluorine Chemistry. By *M. Hudlicky*. Plenum Press, New York—London 1971. 1st Edit. xiii 198 pp., numerous figures and 50 tables, bound $ 18.48.

This book appears to be based on the manual published by the same author in the late 1950's, which was translated into German in 1960 under the title: "Chemie der organischen Fluorverbindungen". The great value of this fundamental monograph on organic fluorine chemistry lay in the concise summary of methods, preparation routes, and reactions.

In comparison with the standard work, which has become a "classic", the present book contains no fundamental changes. The first few chapters deal with fluorinating agents and their use. The chapter "Analysis of Organic Fluorine Compounds" has been placed earlier in the book, and now contains brief notes on IR, mass, and fluorine NMR spectroscopy.

The longest chapter deals with the reactions of organic fluorine compounds. An introductory section on reaction mechanisms presents a discussion of the inductive, mesomeric, steric, and hyperconjugation effects for the interpretation of the reactivity of fluorinated organic compounds, which is rather superficial. The section "Hyperconjugation", for example, makes no mention of the fact that this model has no physical significance. Valid theories that should also have been used for the explanation of mesomeric effects" are not considered.

In the reviewer's opinion, any survey of this special field, however detailed, is of little value at present without a fairly profound discussion of the broader relationships. The book can therefore be recommended at best as a collection of facts.

H. J. Scholl [NB 116 IE]

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Carbocations and Electrophilic Reactions[1][**]

By George A. Olah[*]

The general concept of carbocations encompasses all cations of carbon containing compounds which can be differentiated into two distinct classes: trivalent ("classical") carbenium ions and pentacoordinated ("nonclassical") carbonium ions. In this paper the preparation and structural study (by NMR, IR, Raman and ESCA spectroscopy) of stable carbenium ions and carbonium ions are discussed. As is well known, trivalent carbenium ions play an important role in electrophilic reactions of π- and n-donor systems. Similarly, pentacoordinated carbonium ions are the key to electrophilic reactions of σ-donor systems (single bonds). The ability of single bonds to act as σ-donor lies in their ability to form carbonium ions *via* triangular two electron, three-center bond formation. Consequently there seems to be no principle difference between the electrophilic reactions of π- and σ-bonds except that the former react more easily, even with weak electrophiles, whereas the latter necessitate more severe conditions. The role of carbocations in electrophilic reactions of π- and σ-donor systems is discussed.

1. General Concept

1.1. Definition and Differentiation of Carbenium Ions and Carbonium Ions

The concept of carbocations (it seems to be the logical name for all cationic carbon compounds since the negative ions are called carbanions), with exception of the early isolation of highly stabilized triarylcarbenium ion salts, had its origin and grew to maturity through kinetic, stereochemical, and product studies of a wide variety of reactions, especially unimolecular nucleophilic substitutions and eliminations[2]. Leading investigators such as *Meerwein, Ingold, Hughes, Whitmore, Bartlett, Nenitzescu, Winstein,* and others have contributed fundamentally to the development of modern carbenium ion theory, *i.e.* to the concept of electron deficient cationic intermediates. Direct observation of stable, long-lived carbenium ions, generally in highly acidic (superacid) solvent systems, has become possible only in recent years[3].

Based on our continuing study of carbocations by direct observation of long-lived species, it became increasingly apparent that the carbocation concept is much broader than previously realized and necessitates general definition. Such a definition is offered, therefore, based on the realization that *two distinct classes of carbocations exist*[4]:

a) *Trivalent ("classical") carbenium ions* containing an sp^2-hybridized *electron deficient* central carbon atom (with six electrons in the valence shell), which, in the absence of constraining skeletal rigidity or steric interference, tends to give a planar (or close to planar) arrangement with the three directly bound atoms. (It should be noted that sp-hybridized, linear acyl cations and vinyl cations also show substantial electron deficiency on carbon.)

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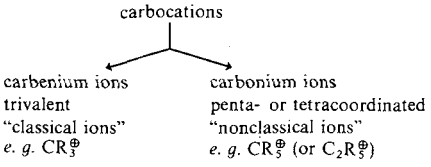
[**] This memoir will also be published as a separate brochure, copies of which can be ordered from Verlag Chemie GmbH, D-694 Weinheim, Postfach 129/149 (Germany) or John Wiley & Sons Inc., 605 Third Avenue, New York, N. Y. 10016 (USA). A German version is also available from Verlag Chemie GmbH.

b) *Penta-(or tetra)coordinated ("nonclassical") carbonium ions*, which contain five or four coordinated carbon atoms (having eight electrons in the valence shell) bound by three single bonds, and a two-electron, three-center bond (the latter being bound either to two additional bonding atoms or involving a carbon atom to which they are also bound by a single bond).

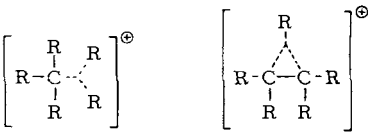


Expansion of the carbon octet *via* 3d-orbital participation does not seem possible; there can be only eight valence electrons in the outer shell of carbon[5]. Thus the covalency of carbon cannot exceed four. Pentacoordination implies a species with five or four ligands within reasonable bonding distance from the central atom[6]. The transition states long ago suggested for S_N2 and S_E2 reactions may represent such cases. However, the direct observation of stable pentacoordinated species in solution was not reported until recently when studies were carried out on long-lived "nonclassical" ions in superacid solvent systems. Moreover, in the past, S_E2 substitution reactions have been mainly restricted to organometallic compounds, *e.g.* organomercurials[7].

Interaction of neighboring groups with the vacant p-orbital of the carbenium ion center can contribute to ion stabilization *via* charge delocalization. Such phenomena can involve atoms with unshared electron pairs (n-donors), C—H and C—C hyperconjugation, bent σ-bonds (as in cyclopropylcarbenium ions) and π-electron systems (direct conjugative or allylic stabilization). Thus trivalent carbenium ions can show varying degrees of delocalization without becoming pentacoordinated carbonium ions. The limiting classes defined do not exclude varying degrees of delocalization, but in fact imply a spectrum of carbocation structures.

In contrast to the rather well-defined trivalent ("classical") carbenium ions, "nonclassical ions"[8] have been more loosely defined. In recent years, a lively controversy has centered on the classical-nonclassical carbonium ion problem[9]. The literature contains numerous contributions to the topic, but no generally accepted definition of nonclassical ions has emerged. Furthermore, no direct experimental means have been recognized for the differentiation of classical and nonclassical ions. The extensive use of "dotted lines" when writing carbonium ion structures has been (rightly) criticized by *Brown*[9d], who carried, however, the criticism to questioning the existence of any σ-delocalized (nonclassical) ion. For these ions, if they exist, he stated "...a new bonding concept not yet established in carbon structures is required".

It is suggested that unequivocal experimental evidence has since been obtained for nonclassical ions such as the norbornyl cation[10], and that the bonding concept required to define "nonclassical ions" is to consider them as penta- or tetracoordinated carbonium ions, of which CH_5^+ (the methonium ion, carbonium ion) is the parent, in the same way as CH_3^+ (methenium ion, methyl cation, carbenium ion) is the parent for trivalent carbenium ions.



For simplicity it is suggested that three-center bonds be depicted by triangular dotted lines drawn from and meeting each other between the three participating atoms; full straight lines are used to symbolize two center, two electron bonds. Such a formulation best illustrates the overlapping bonding orbitals; however, it must be remembered that the point of branching of the dotted line does not represent an additional atom.

Regarding the carbocation concept, it is regrettable that trivalent, planar ions of the type CH_3^+ are generally referred to as carbonium ions in the Anglo-Saxon literature. If the name is considered analogous to other onium ions (ammonium, sulfonium, phosphonium ions, *etc.*), then it should relate to the higher valency state carbocation. The higher valency state carbocations, however, clearly are not the trivalent but the *pentacoordinated cations* of the CH_5^+ type. In the German and the French literature the term "carbenium ion" is frequently used for naming the trivalent cations. Should we consider these latter ions as protonated carbenes, then this naming is indeed correct[11] and in agreement with IUPAC rules for the nomenclature of organic compounds and we could thus *differentiate* quite simply between *carbenium (trivalent)* and *carbonium (penta- or tetracoordinated) ions*[12]. It should be pointed out, however, that "carbenium ion" should be used only for the trivalent ions and not as a generic name for all carbocations. Owing to the wide acceptance of naming all cations of carbon, as carbonium or carbenium ions, we find the use of prefixes for differentiating trivalent and penta- or tetracoordinated is advisable. However, in the future the nomenclature must differentiate quite clearly between trivalent carbenium ions and pentacoordinated carbonium ions.

1.2. Development of Modern Theory: Kinetic and Stereochemical Studies

One of the most daring and fruitful ideas born in organic chemistry was the suggestion that carbocations might be intermediates in reactions that start from nonionic reactants and lead to nonionic covalent products. It was *Meerwein*[13] who in 1922, while studying the kinetics of the rearrangement of camphene hydrochloride to isobornyl chloride, reported the important observation that the reaction rate increased in a general way with the dielectric constant of the solvent. Further, he found that metal chlorides—such as $SbCl_5$, $SnCl_4$, $FeCl_3$, $AlCl_3$, and $SbCl_3$ (but not BCl_3 or $SiCl_4$), as well as dry HCl—which promote the ionization of triphenylmethyl chloride by formation

of ionized complexes, considerably accelerate the rearrangement of camphene hydrochloride. *Meerwein* concluded that the conversion of camphene hydrochloride into isobornyl chloride actually does not proceed by way of migration of the chlorine atom but by a rearrangement of a cationic intermediate. Thus the modern concept of carbocations was born.

In England, starting in the late 1920's, *Ingold* and *Hughes et al.* carried out detailed kinetic investigations on what later became known as nucleophilic substitution at saturated carbon and on polar elimination reactions[14]. The well-known work relating to S_N1 and later to E1 reactions established the carbocation concept. In a series of papers from 1932 onwards *Whitmore*[15] extended *Meerwein*'s rearrangement theory to many organic chemical reactions.

Kinetic and stereochemical evidence helped to establish the role played by carbocations in organic reactions. Generally, however, they were considered only as very short lived species and could not be directly detected by physical means.

1.3. Observation of Stable, Long-lived Ions

The transient nature of carbocations in chemical reactions arises from their extreme reactivity with nucleophiles. By the use of highly acidic and very weakly nucleophilic solvents, it is possible to prevent reactions leading to covalent products; in the last decade or so it has been possible in this way to observe a wide range of *stable*, long-lived carbocations.

2. Preparation and Structure of Stable Trivalent Carbenium Ions

2.1. Alkylcarbenium Ions

2.1.1. Early Unsuccessful experiments

Simple alkylcarbenium ions were, until recently, considered only as transient entities[2] and their existence has been inferred from studies on the course of certain reactions. No reliable physical or chemical method other than that of electron impact measurements were known for the detection of simple alkylcarbenium ions. The formation of organic cations in the gaseous phase by electron bombardment of alkanes, haloalkanes, and other precursors has been widely investigated by mass spectrometry[16]. An analogous direct observation of carbenium ions in solution has not been achieved.

Observation of alkylcarbenium ions (trivalent alkyl cations) such as the trimethylcarbenium ion (*tert*-butyl cation) $(CH_3)_3C^+$ or the dimethylcarbenium ion (isopropyl cation) $(CH_3)_2CH^+$ has thus been a longstanding challenge for many research workers. The occurrence of alkylcarbenium ions in systems of alkyl halides and Lewis acid halides has been inferred from a variety of observations, such as those of vapor pressure depressions of CH_3Cl and C_2H_5Cl in the presence of gallium chloride[17], the electrical conductivity of aluminum chloride in alkyl chlorides[18] and of alkyl fluorides in boron trifluoride[19], as well as the effect of ethyl bromide on the dipole moment of aluminum bromide[20]. However, in no case has a well-defined, stable ionic salt or complex been established, even at very low temperatures.

Rosenbaum and *Symons*[21] recorded the electronic spectra of alcohols and olefins in sulfuric acid. They observed, for a number of simple aliphatic alcohols and olefins, absorption maxima around 290 nm which they ascribed to the corresponding alkylcarbenium ions.

Later, *Finch* and *Symons*[22] reinvestigated the absorption of aliphatic alcohols and olefins in sulfuric acid, and showed that the condensation products formed with acetic acid (used as solvent for the precursor alcohols and olefins) were responsible for the spectra, not the simple alkylcarbenium ions. Protonated mesityl oxide was identified as the species responsible for the absorption at 290 nm in the isobutylene/acetic acid/sulfuric acid system.

Deno et al.[23] carried out an extensive study of the fate of alkyl cations in H_2SO_4 and oleum. They found that equal amounts of a mixture of saturated hydrocarbons (C_4 to C_{18}) that are insoluble in H_2SO_4 and a mixture of cyclopentenyl cations (C_9 to C_{20}) that are soluble in the H_2SO_4 layer are formed. Cyclopentenyl cations exhibit strong ultraviolet absorption at about 300 nm.

It must be concluded, therefore, that earlier attempts to prove the existence of stable, well-defined alkylcarbenium ions were unsuccessful, both in experiments with sulfuric acid solutions as well as with systems from alkyl halides and Lewis acid halides.

2.1.2. Preparation of Carbenium Ions from Alkyl Fluorides in Solutions Containing Antimony Pentafluoride

In 1962 we reported the first direct observation of stable alkylcarbenium ions in solution[24-26]. We obtained the trimethylcarbenium ion (*tert*-butyl cation) when *tert*-butyl fluoride was dissolved in excess antimony pentafluoride, which served both as Lewis acid and solvent. Later the counterion was found to be, under these conditions, primarily the dimeric anion $Sb_2F_{11}^-$[27]; whereas in SbF_5—SO_2 or SbF_5—SO_2ClF solutions, both SbF_6^- and $Sb_2F_{11}^-$ were found.

$$(CH_3)_3CF + (SbF_5)_2 \rightarrow (CH_3)_3C^{\oplus}Sb_2F_{11}^{\ominus}$$

The possibility of obtaining stable alkylcarbenium fluoroantimonate salts from alkyl fluorides (and subsequently other halides) in antimony pentafluoride solution (neat or diluted with sulfur dioxide, sulfuryl chloride fluoride, or sulfuryl fluoride) or in other superacids[28] [particularly FSO_3H—SbF_5 (magic acid®[29]), HF—SbF_5, fluoroantimonic acid, see subsequent discussion) was investigated in detail, our studies extending to all isomeric C_3, C_4 and C_5 alkyl fluorides, as well to a number of higher alkyl halides.

Propyl, butyl, and pentyl fluorides in excess antimony pentafluoride gave the isopropyl *(1)*, *tert*-butyl *(2)*, and *tert*-amyl cations *(3)* (as their fluoroantimonates).

$$C_3H_7F + (SbF_5)_2 \longrightarrow H_3C\text{-}\overset{\oplus}{C}H\text{-}CH_3 \quad Sb_2F_{11}^{\ominus} \qquad (1)$$

$$C_4H_9F + (SbF_5)_2 \longrightarrow H_3C\text{-}\overset{\oplus}{C}(CH_3)\text{-}CH_3 \quad Sb_2F_{11}^{\ominus} \qquad (2)$$

$$C_5H_{11}F + (SbF_5)_2 \longrightarrow H_3C\text{-}\overset{\oplus}{C}(CH_3)\text{-}C_2H_5 \quad Sb_2F_{11}^{\ominus} \qquad (3)$$

The secondary butyl and amyl cations can be observed at low temperatures, but they rearrange readily to more stable tertiary ions.

Generally, the most stable tertiary or secondary carbenium ions are eventually observed on starting from any of the isomeric alkyl fluorides in superacidic solvent systems. Rearrangement to these more stable ions can be studied, starting from very low temperatures.

2.1.3. NMR-Spectra

One of the most powerful tools in the study of carbenium ions is nuclear magnetic resonance spectroscopy. The main feature of the proton NMR spectra of alkyl fluorides in antimony pentafluoride is the substantial deshielding of the protons in the carbenium ions as compared with in the starting alkyl fluorides (Fig. 1 and Table 1) and the absence of H—F coupling.

In order to prove that stable alkylcarbenium ions, and not exchanging donor-acceptor complexes were obtained, we investigated the ^{13}C nuclear magnetic resonance of the potentially electropositive carbenium carbon atom in alkylcarbenium ions[30].

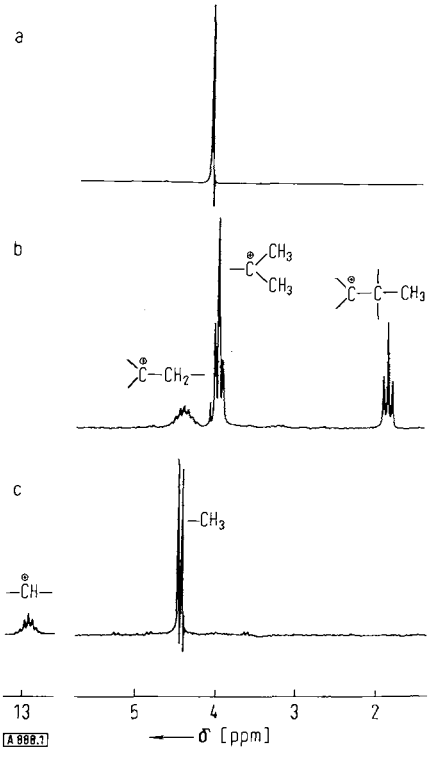


Fig. 1. ^1H-NMR spectra of: a) the *tert*-butyl cation *(2)* [trimethylcarbenium ion, $(CH_3)_3C^+$]; b) the *tert*-amyl cation *(3)* [dimethylethylcarbenium ion, $(CH_3)_2C^+—C_2H_5$]; c) the isopropyl cation *(1)* [dimethylcarbenium ion, $(CH_3)_2C^+H$]. (60 MHz, $SbF_5—SO_2ClF$ solution, $-60°C$.)

The ^{13}C chemical shift of C^+ in the *tert*-butyl cation $(CH_3)_3{}^{13}C^+$ in $SO_2ClF—SbF_5$ solution at $-20°C$ is $\delta_{^{13}C} = -135.4$ (with reference to capillary $^{13}CS_2$, as given throughout this review), the long-range coupling constant (J_{CCH}) to the methyl protons being 3.6 Hz.

Under identical conditions the ^{13}C chemical shift of the C^+ in the isopropyl cation is $\delta_{^{13}C} = -125.0$, and the long-range coupling to the methyl protons is 3.3 Hz (Fig. 2).

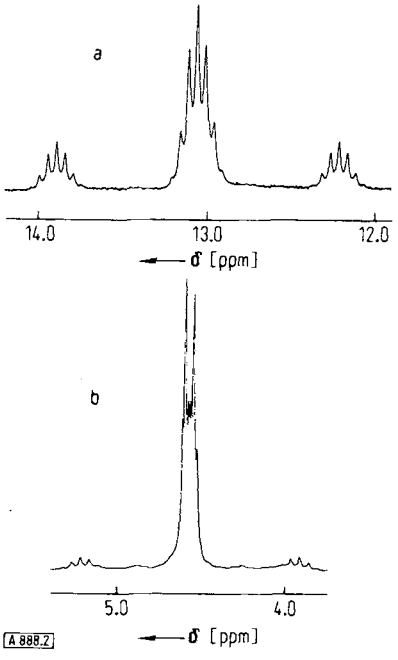


Fig. 2. 100-MHz ^1H-NMR spectrum of the isopropyl cation generated from isopropyl chloride with a 50% ^{13}C enrichment of C-2, in $SO_2ClF—SbF_5$ solution. The spectrum was recorded at $-60°C$. Figure 2a shows the methine region and consists of a septuplet ($J_{HH} = 5$ Hz) with ^{13}C satellites 84.5 Hz on either side of the main resonance ($J_{CH} = 169$ Hz). Figure 2b shows the methyl region. The ^{12}C species gives a doublet in this region while the ^{13}C-labeled ions give a doublet of doublets due to the long-range CCH coupling of 3.3 Hz. Some scrambling of the ^{13}C label into the methyl groups is apparent in this spectrum giving small pentuplets 65.5 Hz on either side of the main resonance. The structure of these satellites arises from the fact that the three- and four-bond proton-proton coupling constants are similar in magnitude (5 and 6 Hz).

The direct $^{13}C—H$ coupling is 169 Hz (a good indication of the sp^2 hybridization of the carbenium carbon atom is obtained from the apparent linear relation of the coupling constant with the hybridization; the electron-deficient carbon atom shows 33.8% s-character). The long-range, proton-proton coupling constant is 6.0 Hz (see Fig. 3).

Substitution of the methyl group in the *tert*-butyl cation by hydrogen thus causes a shielding of the C^+ (upfield shift of the $^{13}C^+$ signal of about 10.4 ppm). If a direct relation between ^{13}C shifts and electron density at C^+ exists, then it could be taken that the central carbon atom in the *tert*-butyl cation is slightly more positive than that in the isopropyl cation. Otherwise the difference can be accounted for in terms of a substituent effect (*i.e.* CH_3 *vs.* H).

The ^{13}C chemical shift of C^+ in the *tert*-amyl cation $[C_2H_5C^+(CH_3)_2]$ is $\delta_{^{13}C} = -139.4$, *i.e.* C^+ is more strongly deshielded (shift downfield of *ca.* 4 ppm) than C^+ in the

tert-butyl cation. This shift difference is much smaller than the 17 ppm found in the case of the related alkanes, although the shift observed is in the same direction.

It should, however, be pointed out that other factors than electron density can also affect the chemical shifts; thus no quantitative conclusion relating to charge densities can be established from the NMR data.

in the *tert*-butyl cation, than on the carbenium center of the isopropyl cation (naturally, this relates only to the gas phase).

It is difficult to interpret the observed large deshieldings and coupling-constant values in any way other than as a direct proof that (i) the central carbon atoms involved in the carbenium ion are sp^2-hybridized, and (ii) that,

Table 1. Characteristic NMR parameters of alkylcarbenium ions in SbF_5—SO_2ClF solution at −70 °C.

Ion	^{1}H-NMR (δ [ppm]) $CH^{\oplus}$	$J_{\oplus CH}$	$J_{\oplus CCH}$	α-CH_2	α-CH_3	β-CH_3	^{13}C-NMR (δ [ppm]) $C^{\oplus}$	α-CH_3
$(CH_3)_2CH^{\oplus}$ (1)	13	169	3.3		4.5		−125.0	132.8
$(CH_3)_3C^{\oplus}$ (2)			3.6		4.15		−135.4	146.3
$(CH_3)_2C^{\oplus}C_2H_5$ (3)				4.5	4.1	1.94	−139.2	150.1
$H_3CC^{\oplus}(C_2H_5)_2$ (4)				4.44	4.16	1.87	−139.4	150.8

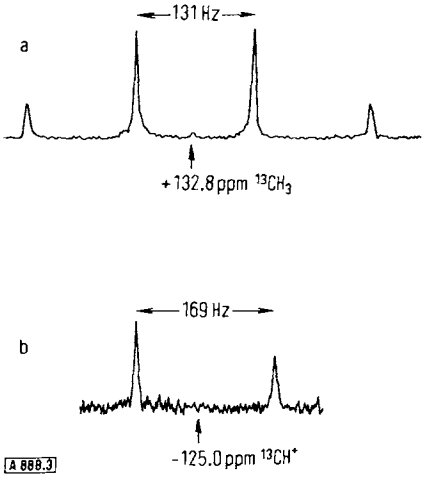


Fig. 3. 25-MHz ^{13}C-INDOR spectrum [30a] of the isopropyl cation. The spectra were obtained at −20 °C by monitoring the signal intensity of the ^{13}C satellites shown in Figure 2 while sweeping the irradiating frequency. The peaks observed are the result of splitting of the satellite due to "tickling" of connected ^{13}C transitions. Figure 3a shows the quartet corresponding to the methyl ^{13}C and Figure 3b the doublet from the methine ^{13}C. The latter spectrum was obtained from the low-field ^{13}C satellite in the proton spectrum. The low-field ^{13}C transition is connected regressively and the high-field ^{13}C transition connected progressively to this transition leading to the observed asymmetry of the ^{13}C-INDOR spectrum. This asymmetry is particularly apparent in C-INDOR spectra obtained using a low-amplitude "tickling" field.

The total shielding constant σ for a particular nucleus can be regarded as the sum of three terms

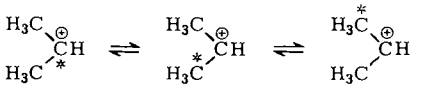
$$\sigma = \sigma_d + \sigma_p + \sigma'$$

where σ_d is the diamagnetic term, σ_p the paramagnetic term, and σ' the term arising from neighboring groups. For a carbon nucleus the dominant paramagnetic contribution is affected principally by charge polarization, variation in bond order, and the average excitation energy. The relative significance of each factor must be considered.

It is interesting to note that theoretical calculations indicate higher positive charge density on the carbenium center at the same time, the carbon atom carries a substantial positive charge.

Table 1 lists the parameters of the ^{1}H- and ^{13}C-NMR spectra of the cationic centers of a few secondary and tertiary carbenium ions. The main points to be noted are the downfield chemical shifts ($\delta_{^{13}C}$) which point to extensive positive character and the coupling constants (J_{CH}) indicative of sp^2-hybridization.

When the isopropyl cation was generated from 50%-labeled [2-^{13}C]-2-chloropropane by dissolution in SO_2ClF—SbF_5 at −60 °C, equilibration of the ^{13}C labeling occurred with a half-life of 1 hour; after several hours the ^{13}C labeling was distributed equally among the three carbons ("scrambling"). This observation suggests involvement of protonated cyclopropanes in the carbon scrambling process (see below). Similar scrambling was observed in the *sec*-butyl and *tert*-amyl cations (*Saunders*[31]).



2.1.4. Infrared and Raman Spectra

Infrared and Raman spectra of the stable alkylcarbenium ions were also recorded[25, 32] and are in complete agreement with the carbenium structure of the ions. The IR spectra of these ions and of their deuterated analogs correspond to the spectra predicted by calculations based on selected molecular models and force constants. Thus, vibrational spectra can also be used in the identification of stable carbenium ions.

Laser Raman spectroscopy is another powerful tool in the study of carbocations. Since Raman spectra give valuable information on symmetry, these spectra help to establish in detail the structures of the ions and their configurations. Raman spectroscopic data provide strong evidence,

for example, that the trimethylcarbenium ion in magic acid[29] prefers a conformation leading to overall C_{3v} point group symmetry (Table 2). Thus, the $\overset{+}{C}(CH_3)_3$ ion possesses a planar $C^+(C_3)$ carbon skeleton with one hydrogen atom of each CH_3 group above the plane of the carbon atoms. The other two hydrogen atoms are arranged symmetrically below this plane to the right and left of the C_3 axis. Raman spectra observed for the *tert*-amyl cation (dimethylethylcarbenium ion), the pentamethylethyl cation (dimethyl-*tert*-butylcarbenium ion), and the dimethylisopropylcarbenium ion also show similar structure (Fig. 4). Raman and IR spectroscopic studies thus provide, in addition to ^{13}C-NMR data, direct evidence for the planar (or near planar) carbenium center of alkylcarbenium ions.

Table 2. Raman and IR frequencies of the *tert*-butyl cation and [D_9]-*tert*-butyl cation and their correlation with those of $(CH_3)_3B$ and $(CD_3)_3B$.

Species	Frequency of vibration [cm^{-1}]											
	$\nu_1, \nu_{12}, \nu_7, \nu_{19}$	ν_2, ν_{13}	ν_{21}	ν_{14}	ν_{15}	ν_{17}	ν_5	ν_{16}	ν_6	ν_9	ν_{10}	ν_{18}
$(CH_3)_3C^{\oplus}$ (2)	2947	2850		1450		1295			667		347	306
$(CH_3)_3B$	2975	2875	1060	1440	1300	1150	906	866	675	973 (486?)	336 [a]	320
$(CD_3)C^{\oplus}$	2187	2090		1075		980			720		347	300
$(CD)_3B$	2230	2185		1033	1018	1205			620	870	(289) [b]	(276) [b]

[a] IR frequency.
[b] Calculated.

to condensation products or cyclic allylic ions and not to the simple alkylcarbenium ions[34].

2.1.6. ESCA Spectra

ESCA spectroscopy[35] is an extremely useful method for the investigation of carbocations[36]. Within such molecules the positive charge is generally unequally distributed over different atoms of the carbon skeleton. Consequently, the core electrons of these atoms are differently screened

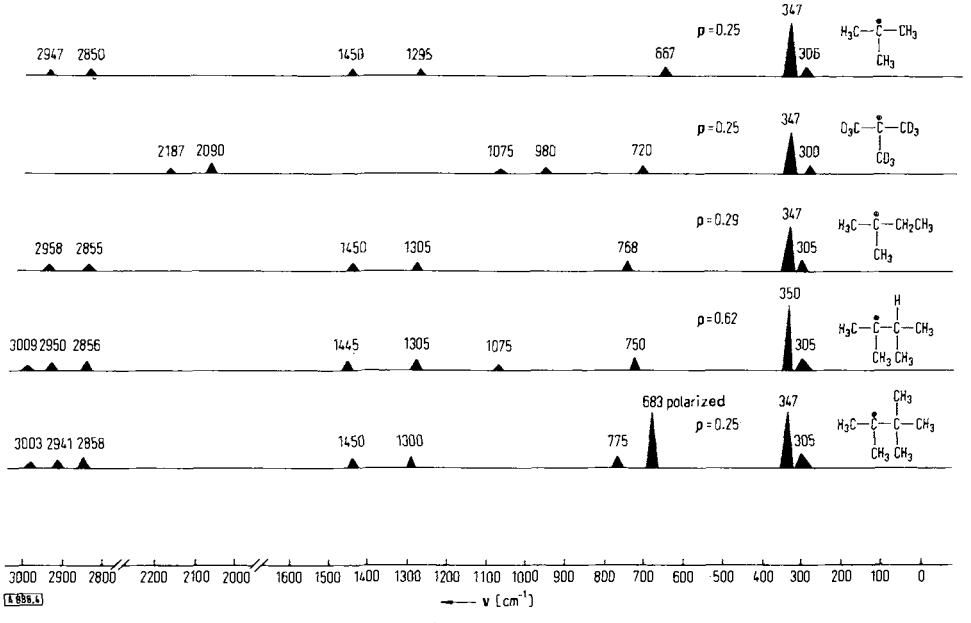


Fig. 4. Schematic representation of Raman spectra of alkyl cations

Evidence for planarity or near planarity of the sp^2 center of trivalent alkylcarbenium ions thus comes from the combined results of NMR (^{1}H and ^{13}C), IR, and Raman spectroscopy[30,32].

2.1.5. UV Spectra

The observation of stable alkylcarbenium ions in antimony pentafluoride and related superacid solutions also opened up the possibility of investigating the UV and visible spectra of such solutions. *Waack*, *Pittman*, and *I* reported[33] that solutions of alkylcarbenium ions in FSO_3H—SbF_5 solutions at −60 °C showed no absorption maxima above 210 nm. In view of this observation, it is highly probable that previous claims relating to a 290 nm absorption of alcohols and olefins in sulfuric acid solutions were due

and show increasing binding energies with increasing positive charge on the C atoms. With correspondingly large positive charge on the carbocationic center the energy differences are large enough to give rise to separate 1s-level photoelectron lines.

In contrast measurements of carbon 1s electron binding energies in several hydrocarbons yielded a rather narrow range of chemical shifts. For instance, one cannot distinguish between the carbon atoms of neopentane and those of benzene, for their 1s binding energies are virtually the same (290.4 eV). Ethane (290.6 eV), ethylene (290.7

eV), and acetylene (291.2 eV) carbon 1s binding energy differences are well below the presently attainable resolution with ESCA measurements.

These results are in agreement with theoretical expectations. Core electrons are barely affected unless their screening against nuclear attraction is modified by a significant change in the outer (valence) electron shell. In other words, core electron binding energies are mainly dependent on the formal charge of the corresponding atom and on the electronegativity of attached atoms or groups of atoms. The fact that such factors are minimal in hydrocarbons accounts for the small differences described above.

Since ESCA spectroscopy is a 'surface' method the recording of the spectra of the carbenium ions was carried out on frozen superacid solutions or on isolated salts; they were recorded at liquid nitrogen temperature[36].

The binding energies E_b (defined as differences between the Fermi level and the 1s atomic level energies) are given by the equation

$$E_b = E_{h\nu} = E_{kin} - \Phi_s$$

where $E_{h\nu}$ is the energy of the exciting radiation (*e.g.* $Al_{K\alpha}$ X-rays), E_{kin} is the measured kinetic energy of the photoejected electron, and Φ_s is the spectrometer work function (the energy necessary to bring the electron from the Fermi level to the free-electron level). The 1s-electron spectrum (ESCA spectrum) of the *tert*-butyl cation is shown in Figure 5.

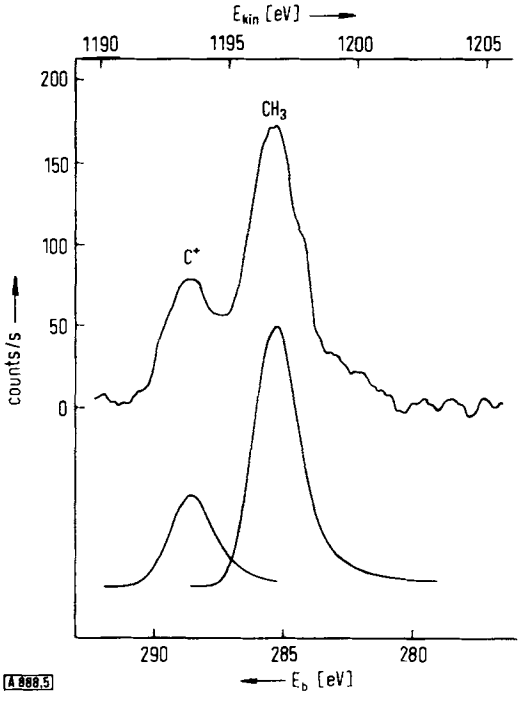


Fig. 5. Carbon 1s electron spectrum (ESCA) of the *tert*-butyl cation (*2*). E_b = binding energy, E_{kin} = kinetic energy.

The upper trace in Figure 5 exhibits two clearly separated peaks with a separation of $dE_{b+C-C} = 4 \pm 0.2$ eV. The lower trace represents the result given by a curve resolver. The peak area ratio is 1:3.

The experimentally determined carbon 1s binding energy difference between the carbenium ion center and the remaining three carbon atoms lies within the limit of that predicted by *ab initio* quantum mechanical calculations (4.45 eV). Comparable results were obtained in experiments carried out in collaboration with *Mateescu* on a series of other alkylcarbenium ions, such as the *tert*-amyl cation (*3*) ($dE_{b+C-C} = 4 \pm 0.2$ eV).

2.1.7. Preparation of Carbenium Ions from Other Precursors

Alkylcarbenium ions can be formed not only from halides (the earlier investigation of generation from alkyl fluorides was later extended to alkyl chlorides, bromides, and even iodides) but also from other precursors such as olefins in superacids like HF—SbF_5 and FSO_3H—SbF_5[37, 38].

$$RCH{=}CH_2 \xrightarrow[HF\text{-}SbF_5]{FSO_3H\text{-}SbF_5} \overset{\oplus}{R}CH\text{-}CH_3$$

Tertiary and reactive secondary alcohols in superacids like FSO_3H—SbF_5 (magic acid®[29])[34], FSO_3H, and SbF_5—SO_2—(SO_2ClF) also ionize to the corresponding stable carbenium ions[39]. The generation of alkylcarbenium ions from alcohols indicates the great advantages of increasing acidity and of using acid systems with low freezing points. *Deno*[23] showed that the use of sulfuric acid and oleum results in formation of cyclized allylic ions from simple aliphatic alcohols. If the extremely strong acid FSO_3H—SbF_5 ("magic acid"®) is used these alcohols can be ionized to the corresponding tertiary and secondary alkylcarbenium ions without further rearrangements taking place.

$$(CH_3)_3C\text{-}OH \xrightarrow[-H_2O]{FSO_3H\text{-}SbF_5} (CH_3)_3C^{\oplus}$$

Primary and less reactive secondary alcohols are protonated in FSO_3H—SbF_5 solution at low temperatures (−60 °C) and show very slow or no proton exchange with the superacid[40].

$$H_3C\text{-}CH_2\text{-}CH_2OH \underset{-H^{\oplus}}{\overset{+H^{\oplus}}{\rightleftharpoons}} H_3C\text{-}CH_2\text{-}\overset{\oplus}{C}H_2OH_2$$

$$H_3C\text{-}\underset{OH}{CH}\text{-}CH_3 \underset{-H^{\oplus}}{\overset{+H^{\oplus}}{\rightleftharpoons}} H_3C\text{-}\underset{\oplus OH_2}{CH}\text{-}CH_3$$

Temperature-dependence studies of the NMR spectra allow the kinetics of dehydration of protonated alcohols to the corresponding carbenium ions to be followed[41].

$$H_3C\text{-}CH_2\text{-}CH_2\text{-}CH_2OH \xrightarrow[-60\,^{\circ}C]{FSO_3H\text{-}SbF_5\text{-}SO_2} H_3C\text{-}CH_2\text{-}CH_2\text{-}\overset{\oplus}{C}H_2OH_2$$

$$\xrightarrow{\Delta,\ H^{\oplus}\ /\ -H_3O^{\oplus}} [H_3C\text{-}CH_2\text{-}CH_2\text{-}CH_2^{\oplus}] \rightarrow (CH_3)_3C^{\oplus}$$

Antimony pentafluoride itself (neat or in SO_2 or SO_2ClF solution) ionizes alcohols smoothly to alkylcarbenium ions.

$$R{-}OH \xrightarrow{SbF_5} R^{\oplus}SbF_5OH^{\ominus}$$

We have found that difficulties in the ionization of primary (and less reactive secondary) alcohols at low temperatures can be overcome, in some cases, if the alcohols are first converted with thionyl halides or carbonyl halides into the corresponding haloformates *(5)* or halosulfites *(6)*, which then readily ionize in SbF_5—SO_2 solution and lose CO_2 or SO_2 (fragmentation ionization)[37,42].

$$ROH \xrightarrow{COX_2} \underset{(5)}{RO{-}\overset{\overset{O}{\|}}{C}{-}X} \xrightarrow{SbF_5\text{-}SO_2} R^{\oplus}SbF_5X^{\ominus} + CO_2$$

$$ROH \xrightarrow{SOX_2} \underset{(6)}{RO{-}\overset{\overset{O}{\|}}{S}{-}X} \xrightarrow{SbF_5\text{-}SO_2} R^{\oplus}SbF_5X^{\ominus} + SO_2 \qquad X = Cl, F$$

Aliphatic ethers such as *(7)* are protonated in strong acids, and subsequently cleaved (at higher temperatures) to alkylcarbenium ions[43].

$$\underset{(7)}{H_3C{-}O{-}CH_2{-}CH_2{-}CH_2{-}CH_3} \xrightarrow[-60\,^{\circ}C]{FSO_3H\text{-}SbF_5} H_3C{-}\overset{\overset{\oplus}{H}}{\underset{|}{O}}{-}CH_2{-}CH_2{-}CH_2{-}CH_3 \xrightarrow[H^{\oplus}]{\Delta} H_3C\overset{\oplus}{O}H_2 + [H_3C{-}CH_2{-}CH_2{-}CH_2^{\oplus}] \longrightarrow (CH_3)_3C^{\oplus}$$

The protonation and subsequent ionization of mercaptans (thiols) and sulfides have been studied in a similar way[44].

Superacids such as FSO_3H—SbF_5 act as very effective hydrogen abstracting agents, allowing the generation of carbocations from saturated hydrocarbons[45].

$$H_3C{-}\underset{\underset{CH_3}{|}}{CH}{-}CH_3 \xrightarrow[SO_2ClF]{FSO_3H\text{-}SbF_5} (CH_3)_3\overset{\oplus}{C} + H_2$$

Antimony pentafluoride itself (without addition of FSO_3H or HF) also ionizes alkanes to the corresponding alkylcarbenium ions. Since SbF_5 always contains traces of HF, however, it is questionable whether the reaction is effected by the Lewis acid itself.

Carbenium ions can also be generated by decarbonylation of *tert*-alkyloxocarbenium ions, such as the *tert*-butyloxocarbenium ion (pivaloyl cation) *(8)*[26].

$$(CH_3)_3CCOF + SbF_5 \rightleftharpoons \underset{(8)}{(CH_3)_3CCO^{\oplus}SbF_6^{\ominus}} \overset{\Delta}{\rightleftharpoons} (CH_3)_3C^{\oplus}SbF_5^{\ominus} + CO$$

This reaction corresponds to the reverse of the Koch-Haaf acid synthesis, which is known to involve reaction of carbenium ions with carbon monoxide. Indeed, the pivaloyl cation can be obtained by reaction of the tertiary butyl cation with carbon monoxide[26,46].

Thiols and thioesters (sulfides), like their oxygen analogs, can also be used as starting substances for preparation of alkylcarbenium ions[47]; their ionization in superacids generally necessitates more forcing conditions (higher temperatures). *S*-Alkyl halothioformates *(9)* also form carbenium ions *via* fragmentation ionization[48].

$$RSH \xrightarrow[HF\text{-}SbF_5,\ FSO_3H\text{-}SbF_5]{SbF_5 \text{ or}} R^{\oplus}SbF_5SH^{\ominus}$$

$$\underset{(9)}{RS{-}\overset{\overset{O}{\|}}{C}{-}Cl(F)} \xrightarrow{SbF_5\text{-}SO_2ClF} R^{\oplus}SbF_5Cl^{\ominus}(F) + COS$$

Amines also can be used as precursors for the generation of alkylcarbenium ions. The classical method of deaminative formation of carbenium ions involves some type of diazotization reaction producing an equimolar amount of water.

$$RNH_2 \xrightarrow[-H_2O]{HNO_2} [RN_2^{\oplus}] \longrightarrow R^{\oplus} + N_2$$

This difficulty can be overcome by first converting the amine into the corresponding sulfinylamine *(10)* or isocyanate *(11)*, which is then reacted with stable nitrosyl (NO^+) salts to give the related carbenium ion with evolution of N_2 and SO_2 (or CO_2) instead of water[49].

$$RNH_2 \xrightarrow{SOCl_2} \underset{(10)}{RNSO} + NO^{\oplus}SbF_6^{\ominus} \longrightarrow R^{\oplus}SbF_6^{\ominus} + N_2 + SO_2$$

$$RNH_2 \xrightarrow{COCl_2} \underset{(11)}{RNCO} + NO^{\oplus}SbF_6^{\ominus} \longrightarrow R^{\oplus}SbF_6^{\ominus} + N_2 + CO_2$$

2.1.8. Preparation of Alkylcarbenium Ions in Superacids Not Containing Antimony Pentafluoride

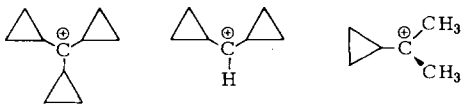
Whereas superacids (such as HF—SbF_5, FSO_3H—SbF_5, CF_3SO_3H—SbF_5 *etc.*) containing antimony pentafluoride are the preferred solvents for obtaining stable alkylcarbenium ions, other superacids such as HF—BF_3, HF—TaF_5 or fluorosulfuric acid can, on occasions, also be used successfully. The stability of carbocations—with exception of tertiary ions—in these solvents is, however, generally lower.

2.2. Cyclopropylcarbenium Ions

Solvolysis studies carried out by *Roberts*[50] and *Hart*[51] showed both the unusual stability of cyclopropylcarbenium ions and the facility with which such ions rearrange.

Cyclopropyl groups bound to the carbocation center have a strong stabilizing effect and effectively delocalize charge. The direct observation of cyclopropylcarbenium ions by NMR spectroscopy provides clear indication of charge delocalization.

The first cyclopropylcarbenium ion observed directly was the tricyclopropylcarbenium ion *(12)*[52]. Its NMR spectrum in H_2SO_4 consists of a single sharp line at $\delta = 2.26$. In the 300 MHz spectrum of a solution in SbF_5—SO_2ClF, however, the signals of the methine and methylene cyclopropyl protons are well resolved[53] (Fig. 6a).



(12) *(13)* *(14)*

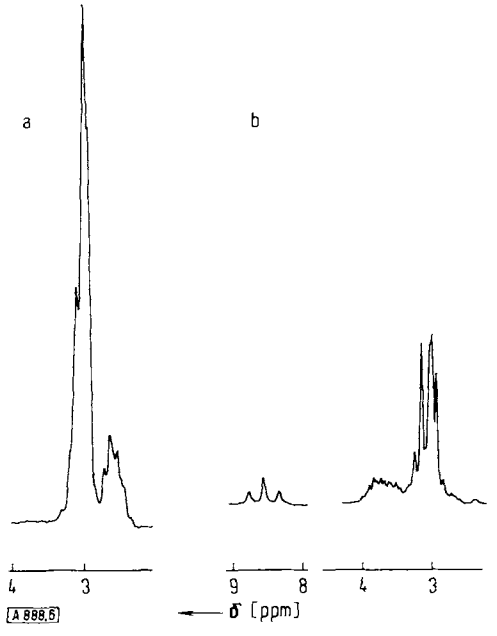


Fig. 6. a) 300-MHz ^{1}H-NMR spectrum of the tricyclopropylcarbenium ion *(12)*; b) 60-MHz ^{1}H-NMR spectrum of the dicyclopropylcarbenium ion *(13)*.

Pittman[54] and *I* have observed several tertiary and secondary cyclopropylcarbenium ions, such as the dicyclopropylcarbenium ion *(13)* (Fig. 6b). The solvent used was usually SbF_5—SO_2 or FSO_3H—SbF_5—SO_2. The ring protons are resolved in the NMR spectrum of each of these ions. Most interesting of these ions is the dimethylcyclopropylcarbenium ion *(14)* (Fig. 7). The two methyl groups are non-equivalent and are separated by 0.54 ppm. Since in uncharged systems the hydrogens lying in the face of the cyclopropane ring experience an upfield shift of 0.3 to 0.5 ppm, we concluded that the cyclopropane ring lies in a plane perpendicular to the plane of the dimethylcarbenium ion center (bisected form).

The plane of the cyclopropane ring lies parallel to the axis of the vacant p orbital of the carbenium carbon atom. In this configuration, one methyl group is *cis* to the cyclopropane ring and the other is *trans*. The *cis* methyl group now experiences the diamagnetic anisotropy of the cyclopropane ring; this accounts for its observed position 0.54 ppm upfield from the *trans* methyl group. The methyl bands do not coalesce at $-30\,^\circ C$, at which temperature

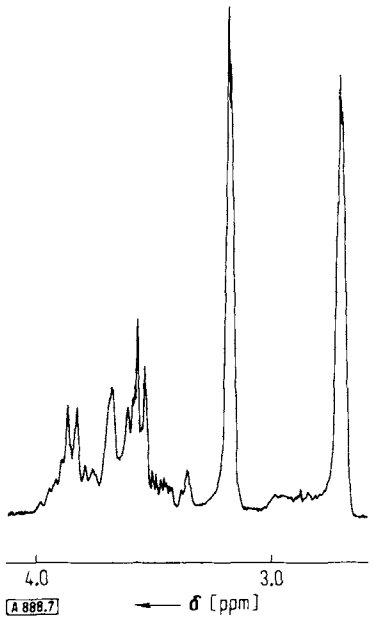


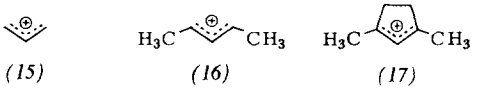
Fig. 7. 100-MHz ^{1}H-NMR spectrum of the dimethylcyclopropylcarbenium ion *(14)*.

ring opening takes place in FSO_3H—SbF_5 solution and the ion undergoes subsequent decomposition reactions. This shows that the cyclopropane ring does not rotate at this temperature, and that the rotational barrier is at least 10 kilocalories per mol. Recently, *Kabakoff* and *Namanworth*[54a] succeeded, using double resonance experiments, in determining the barrier as 13.7 kcal/mol (in SbF_5—SO_2ClF).

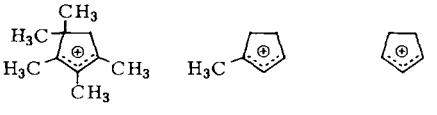
In contrast to the "classical" tertiary and secondary cyclopropylcarbenium ions *(12)*—*(14)* (showing of course substantial charge delocalization over the cyclopropane ring but maintaining the identity of the trivalent ions), primary cyclopropylmethyl cations show entirely different non-classical carbonium ion character (see Section 3).

2.3. Alkenyl Cations

A large number of alkenyl cations has been directly observed, particularly by *Deno* and *Richey*[23,55], *Sorensen*[56], and *Olah*[57] and their co-workers. *Deno* reviewed the chemistry of these ions[23] and the number of known examples has since then increased substantially. Cations of the allylic type are particularly stable. Representative examples which have been observed are the ions *(15)* to *(25)*.



(15) *(16)* *(17)*

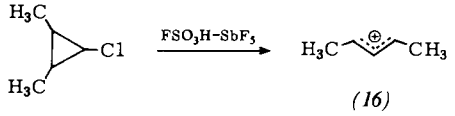


(18) *(19)* *(20)*

(21) (22)

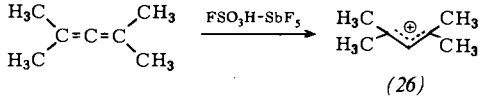
(23) (24) (25)

The opening of halocyclopropanes with the formation of allyl cations such as *(16)* has also been investigated[58-61].



(16)

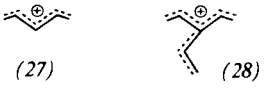
Protonation of certain allenes also leads to allyl cations which are otherwise difficult to obtain from allylic precursors[62,63].



(26)

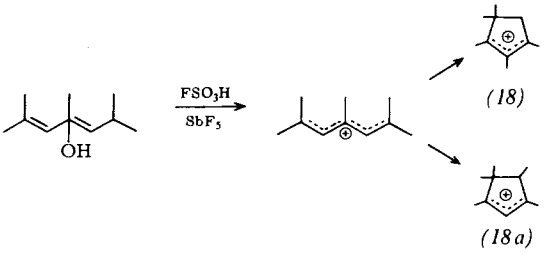
2.4. Alkadienyl and Polyenyl Cations

Deno, *Richey*, and their co-workers[23] have investigated a substantial number of alkadienyl and polyenylic cations. *Sorensen*[64] has reported the observation of the divinyl- *(27)* and trivinylcarbonium ions *(28)*.



(27) (28)

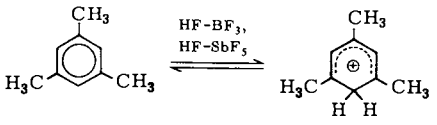
Alkenyl cations show a substantial tendency to cyclize to the more stable cyclic allylic ions such as *(18)* and its isomers *(18a)*. *Pittman*, *Sorensen*, and *I* were able to follow these cyclizations by NMR spectroscopy[65].



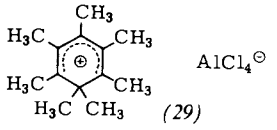
(18) (18a)

2.5. Arenium Ions

Cycloalkadienyl cations, particularly cyclohexadienyl cations (benzenium ions), show remarkable stability. They can be obtained by protonation of aromatic hydrocarbons by strong acids[66-68] and studied advantageously by ^{1}H- or ^{13}C-NMR spectroscopy[69].

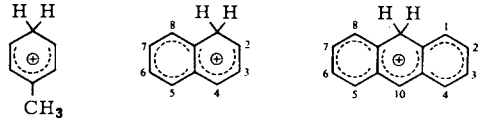


Doering and *Saunders* described the very stable heptamethylbenzenium ion *(29)*[70].



(29)

Figures 8, 9, and 10 show the ^{1}H-NMR spectra of the *p*-toluenium ion *(30)*[69], the naphthalenium ion *(31)*[71] and the anthracenium ion *(32)*[72] as representative examples of arenium ions (which are also of importance as intermediates, usually called σ-complexes, in electrophilic aromatic substitutions).



(30) (31) (32)

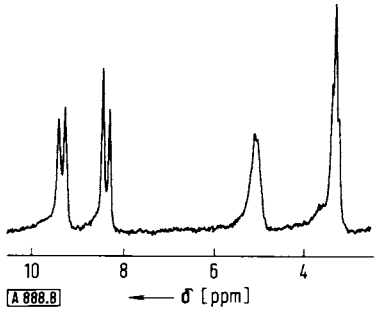


Fig. 8. 60-MHz ^{1}H-NMR spectrum of the *p*-toluenium ion *(30)* at −97 °C.

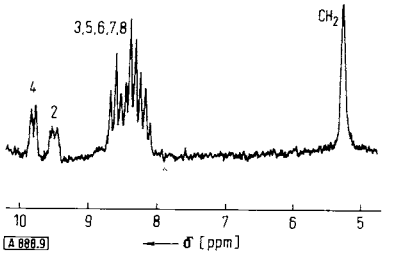
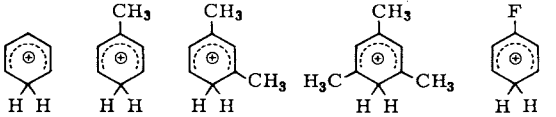


Fig. 9. 100-MHz ^{1}H-NMR spectrum of the naphthalenium ion *(31)* at −90 °C.

Even the parent benzenium ion ($C_6H_7^+$) *(33)* has been observed[73], as have also the isomeric monoalkylbenzenium ions[71,74] and most di-, tri-, tetra- and pentaalkyl



(33) (30) (34) (35) (36)

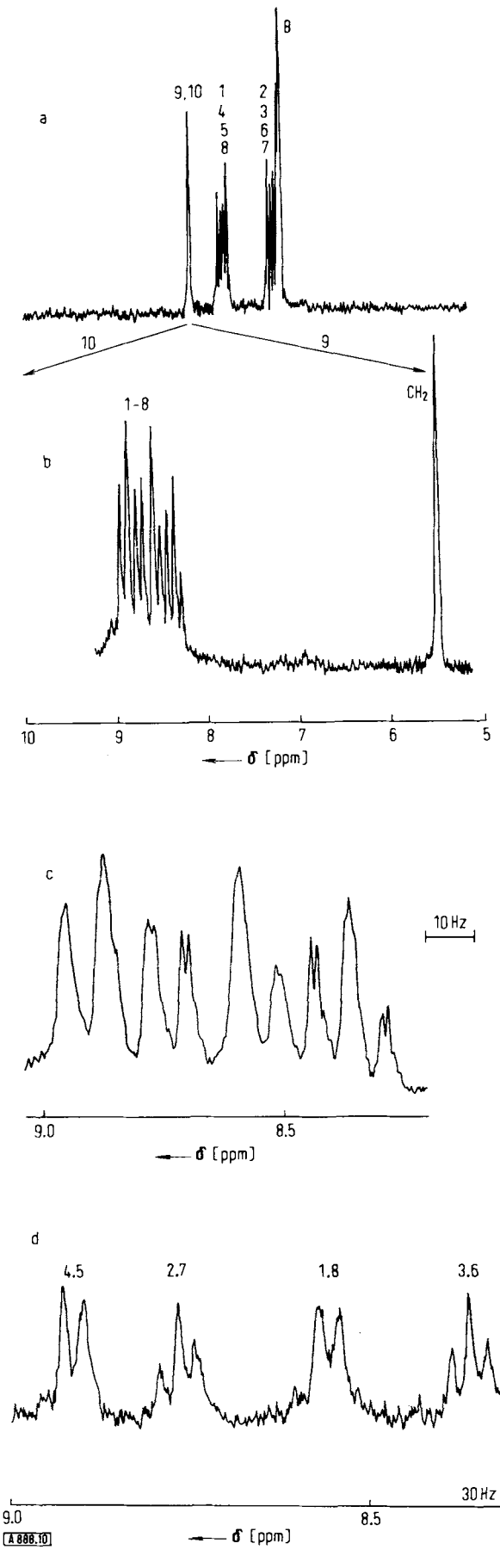
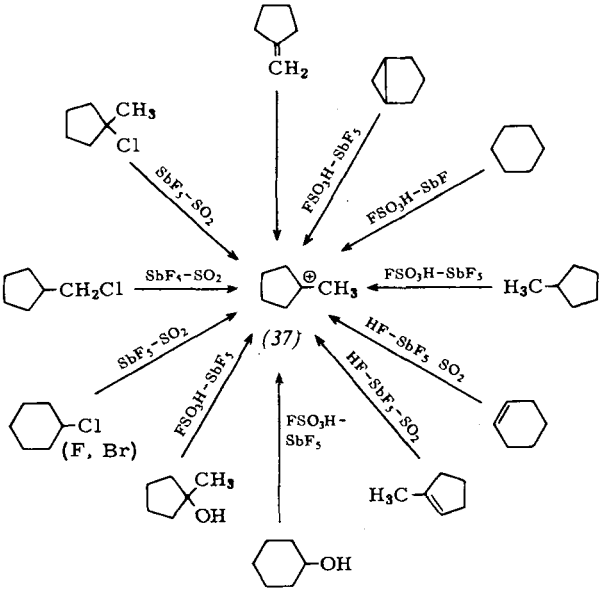


Fig. 10. (a) 100-MHz ^{1}H-NMR spectrum (−55°C) of anthracene in C_6D_6 and (b) of the anthracenium ion *(32)*, B = C_6H_6; (c) part of (b); (d) first order pattern of the 300-MHz ^{1}H-NMR spectrum of the anthracenium ion.

and halobenzenium ions[74]. Some representative ions are *(34)*—*(36)*.

2.6. Cycloalkyl Cations

Tertiary cycloalkyl cations, like the 1-methyl-1-cyclopentyl cation *(37)*, show high stability in superacid solutions. The ion *(37)* can be obtained from a variety of starting substances[75].



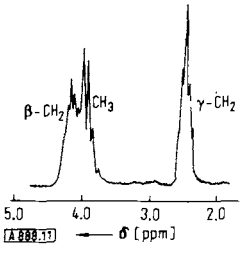
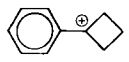


Fig. 11. 60-MHz ^{1}H-NMR spectrum of the 1-methyl-1-cyclopentyl cation *(37)* at −60°C.

It is worthwhile mentioning that not only cyclopentyl but also cyclohexyl compounds give the 1-methyl-1-cyclopentyl cation. This indicates that the tertiary methylcyclopentyl cation is more stable than the secondary cyclohexyl cation, from which it is formed by isomerization.

The cyclopentyl cation shows in its proton magnetic resonance spectrum in SbF_5—SO_2ClF solution, even at 100°C, only a single absorption line at $\delta = 4.68$[38,73]. This observation indicates a completely degenerate ion in which there are only low energy barriers to the consecutive secondary-secondary hydrogen shifts (see below).

The secondary cyclobutyl cation undergoes immediate rearrangement *via* σ-bond delocalization into the equilibrating non-classical cyclopropylmethyl ion system[76] (see Section 3.4). Similar behavior is also observed with the 1-methylcyclobutyl cation. The 1-phenylcyclobutyl cation *(38)* (Fig. 12) on the other hand is a classical tertiary carbenium ion[76].



(38)

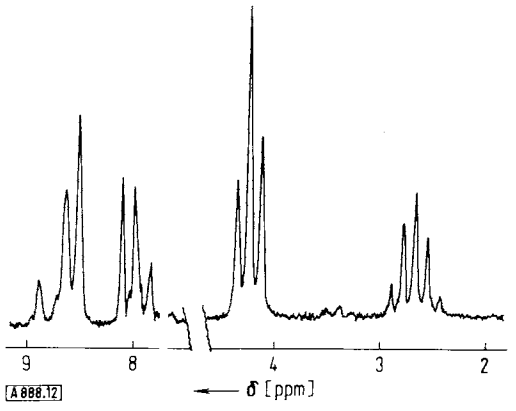
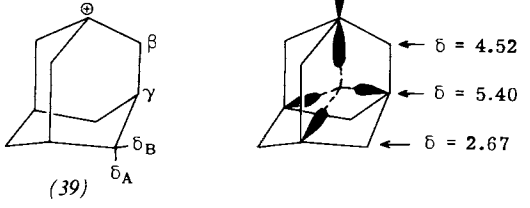


Fig. 12. 60-MHz ^{1}F-NMR spectrum of the 1-phenyl-1-cyclobutyl cation *(38)* at −65°C.

2.7. Bridgehead Carbenium Ions

Bredt's rule in ts original form[77] seems to exclude the possibility of fo mation of positive carbenium ion centers at bridgehead carbon atoms of bicycloalkanes. Indeed, bridgehead halides, such as apocamphyl chloride, proved extremely unreactive under solvolytic conditions[78]. However, 1-bromoadamantane very readily gives the bridgehead carboxylic acid under the usual conditions of the Koch-Haaf acid synthesis[79]. 1-Fluoroadamantane is ionized in SbF_5 to give the stable bridgehead 1-adamantyl cation *(39)*[80,81].



(39)

The ^{1}H-NMR spectrum of the adamantyl cation *(39)* in SbF_5 solution consists of resonances at $\delta = 5.42$, $\delta = 4.50$ and $\delta = 2.67$ with peak areas of 3:6:6. The γ-CH hydrogens are more deshielded, *i.e.* have their resonance at a lower field, than those of the three β-CH_2 groups even though they are farther from the positive carbon. This could be explained by a "cage effect", *i.e.* the lobe of the empty p-orbital overlapping with the backlobes of the three bridgehead C—H bonds, causing their deshielding, or by σ-π hyperconjugation.

A similar effect is indicated in the ^{13}C-NMR spectrum of the 1-adamantyl cation (Fig. 13).

Mateescu, Sipos, Schleyer, and *I* have also observed a series of methyladamantyl cations[81]. The bridgehead "congressane" (diadamantane) cation has also been observed recently[75,81]; it likewise shows the cation cage effect. Although the bridgehead 1-norbornyl cation could not be observed directly, the stable 2-norbornyl cation can be obtained from 1-chloronorbornane in SbF_5—SO_2

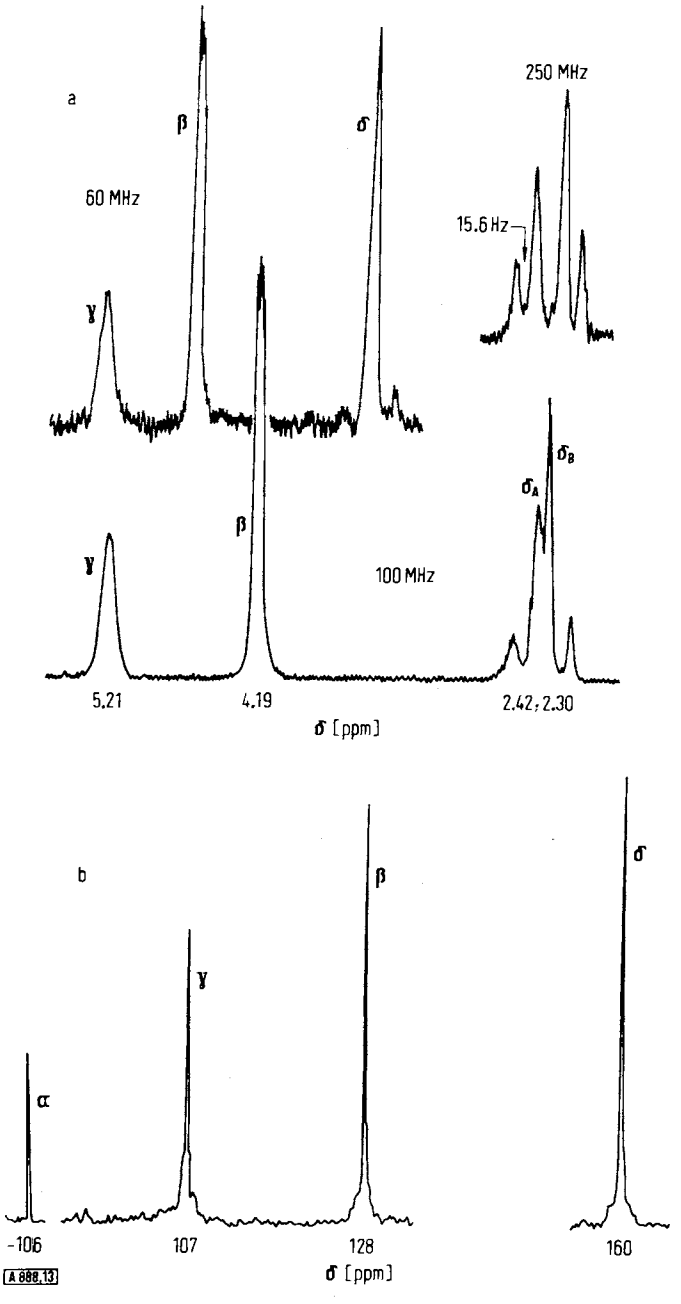
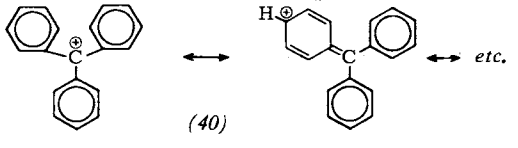


Fig. 13. a) ^{1}H-NMR spectrum of the 1-adamantyl cation at 60 MHz, 100 MHz, and 250 MHz; b) Fourier-transform ^{13}C-NMR of the 1-adamantyl cation (in FSO_3H—SbF_5).

solution[82]. Thus, ionization to the bridgehead carbenium ion must be followed by a fast shift of hydrogen from C-2 to C-1, the driving force for which is obviously the tendency to relieve strain in the carbenium ion.

2.8. Aryl and Alkylarylcarbenium Ions

The first stable long-lived carbenium ion to be observed was the triphenylcarbenium ion *(40)*[83–85] (Fig. 14a).



(40)

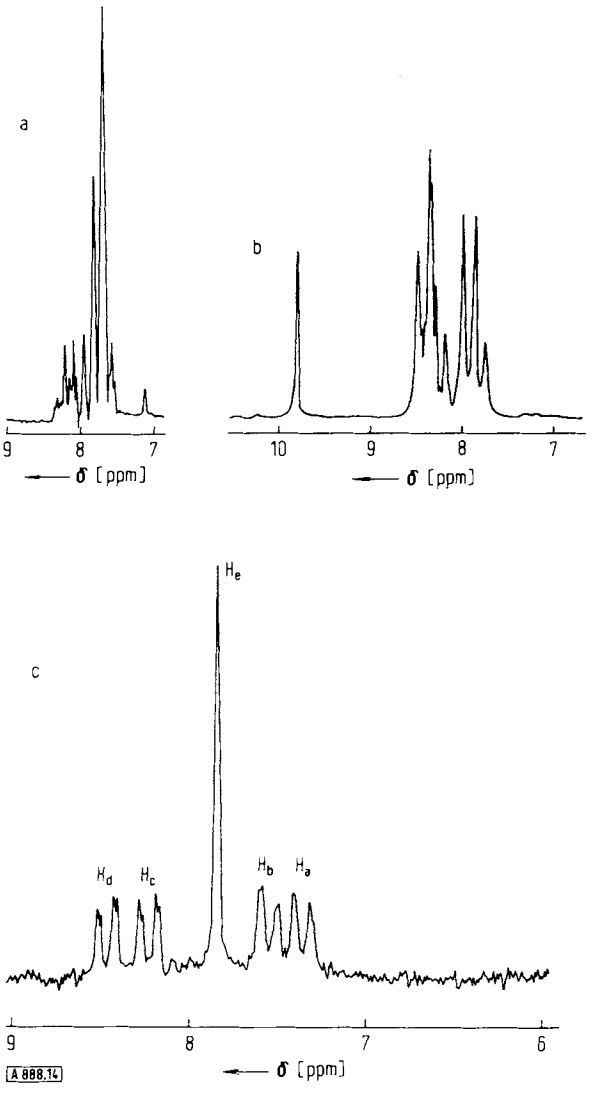
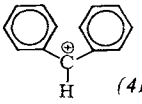


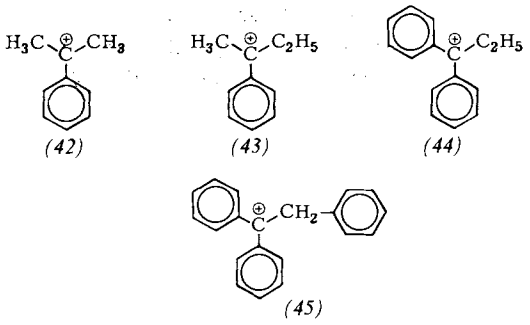
Fig. 14. a) 60-MHz ^{1}H-NMR spectrum of the triphenylcarbenium ion *(40)* (trityl cation); b) 60-MHz ^{1}H-NMR spectrum of the diphenylcarbenium ion *(41)* (benzhydryl cation); c) 100-MHz ^{1}H-NMR spectrum of the 4-methoxyphenylcarbenium ion (*p*-methoxybenzyl cation).

This ion remains the most-investigated carbocation[2] and its propeller-shaped structure has been established beyond doubt. Strong contribution from *para* (and *ortho*) quinonoidal resonance forms in the ion make it probable that these reactive secondary forms contribute strongly to the reactivity of the ion. Diphenylcarbenium ions (benzhydryl cations) are considerably less stable than their tertiary analogs. Although their ultraviolet spectra have been obtained in dilute sulfuric acid solutions[86] the benzhydryl ion *(41)* has only recently been observed in higher concentrations in acid solutions ($ClSO_3H$[87], FSO_3H[88], and FSO_3H—SbF_5[89]) (Fig. 14b).



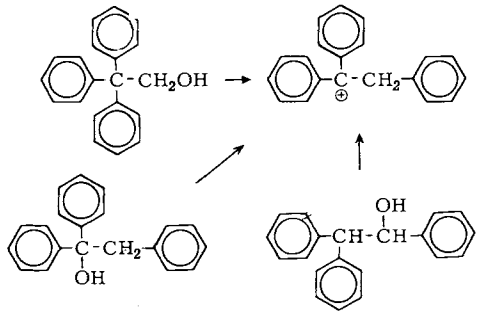
(41)

Solutions of mono- and dialkylarylcarbenium ions can be readily obtained from the corresponding alcohols, olefins, or halides in strong acid media such as H_2SO_4[86], FSO_3H—SbF_5[89], $ClSO_3H$ and FSO_3H[87], and oleum[88]. Representative examples of the cations are *(42)*—*(45)*.

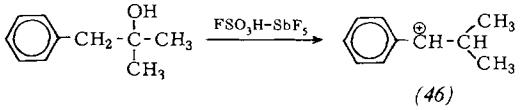


(42) *(43)* *(44)* *(45)*

Because of the high stability of the tertiary ions, these are preferentially formed in the strong acid systems from both tertiary, secondary, and even primary precursors[90].

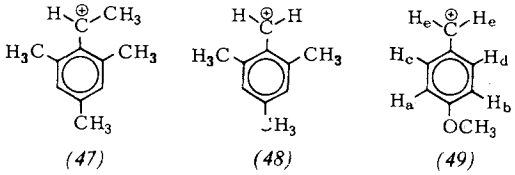


Non-benzylic, tertiary arylalkylcarbenium ions, on the other hand, rearrange to secondary, benzylic ions such as *(46)*.



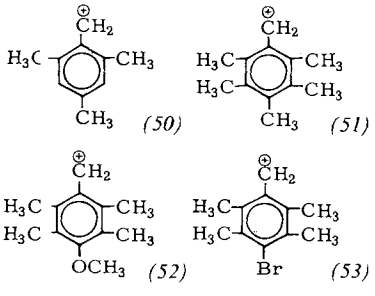
(46)

Suitable substituent groups (which also prevent transalkylations) stabilize even secondary [*e.g. (47)*] and primary benzyl cations [*e.g. (48)*[91,92] and the *p*-methoxybenzyl cation, Fig. 14c].



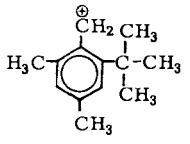
(47) *(48)* *(49)*

The observation of benzyl cations in superacid solutions was only recently achieved[91]. Although the unsubstituted benzyl cation is still elusive, we have observed a number of substituted derivatives such as *(50)*—*(53)*.



(50) *(51)* *(52)* *(53)*

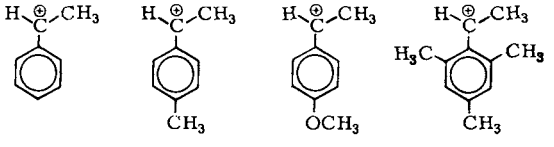
As NMR studies have shown, in benzyl cations like 2,4-dimethyl-6-*tert*-butylphenylcarbenium ion *(54)* a high rotational barrier is observed around the $H_2^+C—C_1$ bond.



(54)

This means that the methylene protons are magnetically non-equivalent[92]. Rearrangement of benzyl cations to tropylium ions, which is claimed to take place in the gas phase (mass spectroscopic measurements) has not been observed in acid solution.

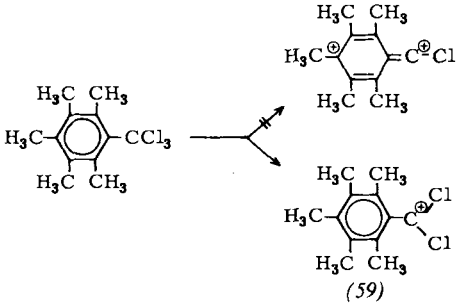
The styryl cation (methylphenylcarbenium ion) *(55)*[93] and a number of substituted methylphenylcarbenium ions *(56)*—*(58)*[85] have also been observed.



(55) *(56)* *(57)* *(58)*

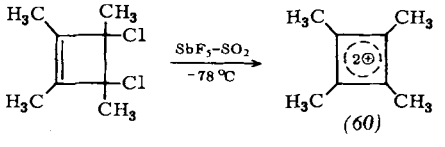
2.9. Dicarbenium Ions

Earlier reports[94] that a dicarbenium ion had been obtained from pentamethyltrichloromethylbenzene have turned out to be incorrect. The species in question is the benzylic dichloropentamethylphenylcarbenium ion *(59)*[95–97].



(59)

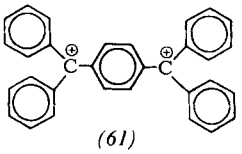
The 1,2,3,4-tetraphenylcyclobutadiene dication has also been reported[98]. However, there is evidence that the ion actually observed was only an equilibrating cyclobutenyl monocation. X-ray crystallographic investigation of the isolated crystalline complex confirm this conclusion[99].



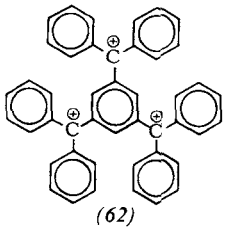
(60)

Recently *Bollinger*, *White*, and *I* succeeded in obtaining the 1,2,3,4-tetramethylcyclobutadiene dication *(60)*[100] and with *Mateescu* we obtained the *bona fide* tetraphenylcyclobutadiene dication[101]. ^1H and ^{13}C nuclear magnetic resonance studies confirmed its structure and the 2π electron aromatic nature, which is similar to the cyclopropenium cations previously prepared by *Breslow*[102].

Hart and *Volz* have shown that if two carbenium centers are separated by a phenyl ring, then a wide variety of di- and tricarbenium ions such as *(61)* and *(62)* can be obtained[103, 104].

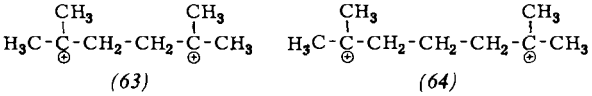


(61)



(62)

We have also prepared simple alkyldicarbenium ions[105], in which the two carbenium ion centers are separated by two or three methylene groups. These ions [*(63)* and *(64)*, Fig. 15] are stable entities in the strongly acidic solvent system ($SbF_5—SO_2$) at low temperature (−60 °C).



(63) *(64)*

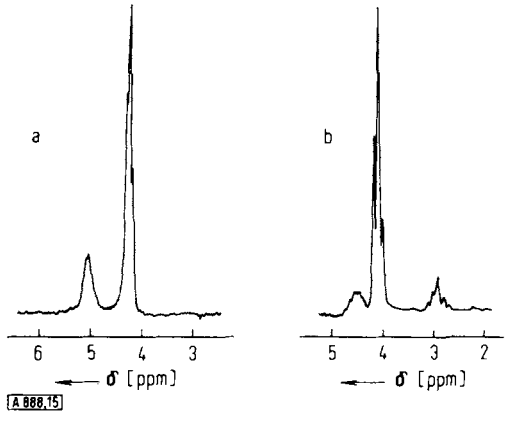
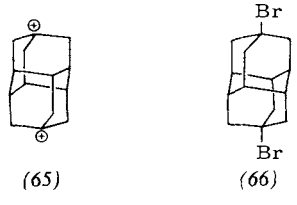


Fig. 15. 60-MHz ^1H-NMR spectra of the alkyldicarbenium ions, a) *(63)* and b) *(64)*.

Dicarbenium ions have also been observed in more rigid cage systems, such as the apical,apical diadamantane dication *(65)*[81] (Fig. 16).



(65) *(66)*

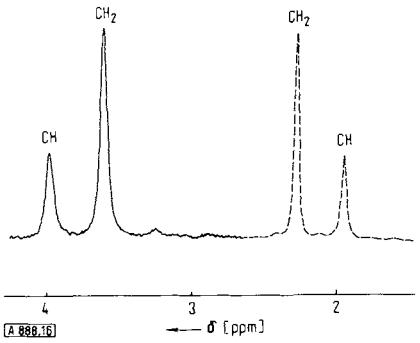
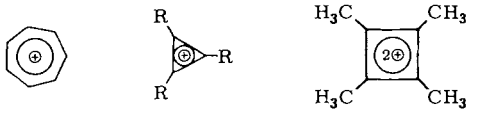


Fig. 16. 100-MHz ^{1}H-NMR spectrum of the apical,apical diadamantane dication *(65)* (———) and the precursor dibromoadamantane *(66)* (– – –).

2.10. Aromatically Stabilized Carbenium Ions

If a carbenium ion is also a Hückeloid aromatic system, resonance causes substantial stabilization. The best known examples of aromatically stabilized carbenium ions are the cycloheptatrienyl cations *(67)* (tropylium ions)[106–108], cyclopropenium ions[102], and the tetramethyl- and tetraphenylcyclobutenium dications[100, 101].

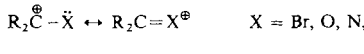


(67) *(68)* *(60)*

Because of their aromatic character, these ions are highly stable. Other examples of aromatically stabilized carbenium ions are also known.

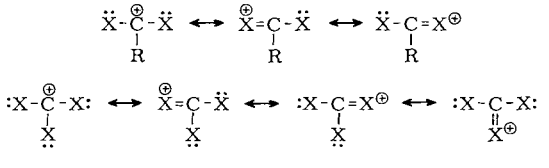
2.11. Heteroatom-Stabilized Carbenium Ions

In contrast to hydrocarbon cations, heteroatom-substituted carbenium ions are strongly stabilized by electron donation from the non-bonded electron pairs of the heteroatoms adjacent to the cationic carbon center:



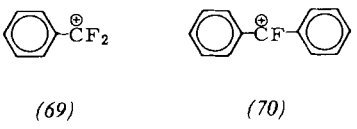
$R_2\overset{\oplus}{C}-\ddot{X} \leftrightarrow R_2C=X^{\oplus}$ X = Br, O, N, S, F, Cl

The stabilizing effect is enhanced when two, or even three, electron-donating heteroatoms coordinate with the electron-deficient carbon atom.



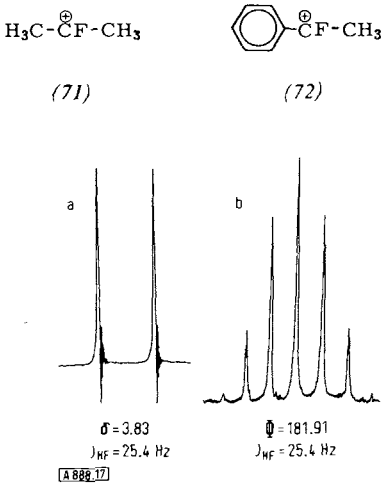
2.12. Halogen as Heteroatom

In 1965, *Cupas, Comisarow*, and *I* reported the first fluorocarbenium ions[109], the phenyldifluorocarbenium ion *(69)* and the diphenylfluorocarbenium ion *(70)*.



(69) *(70)*

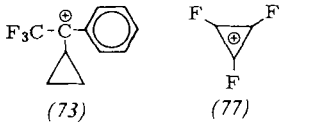
Fluorine has a particular ability to stabilize carbenium ions *via* back-coordination of its unshared electron pairs into the vacant p orbital of the carbon atom. Since ^{19}F magnetic resonance offers an excellent possibility for structural investigations of these ions, extensive work was initiated[110] in this regard. The dimethyl- *(71)* and phenylmethylfluorocarbenium ions *(72)* were *inter alia* prepared and thoroughly investigated[111].



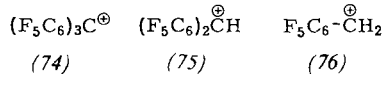
(71) *(72)*

Fig. 17. a) ^{1}H-NMR spectrum of the dimethylfluorocarbenium ion *(71)* at 60 MHz: J_{HF} = 25.4 Hz; b) ^{19}F-NMR spectrum of the same ion at 56.4 MHz: J_{HF} = 25.4 Hz.

Trifluoromethylcarbenium ions such as *(73)*[112] and perfluorophenylcarbenium ions *(74)*—*(76)*[113, 114] have also been investigated. The trifluorocyclopropenium ion *(77)*[115] is also known.



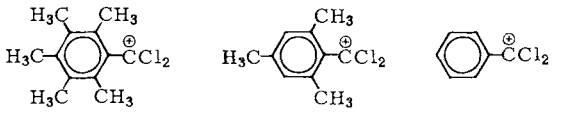
(73) *(77)*



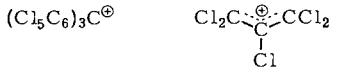
(74) *(75)* *(76)*

Because of the relatively large fluorine resonance shifts, anisotropy and ring current effects play a relatively much smaller role in ^{19}F-NMR spectroscopy than they do in the case of proton resonance. Therefore, as is also true of ^{13}C-NMR spectroscopy, a better correlation between charge distribution and chemical shifts can be obtained than with ^{1}H-NMR spectra.

A series of chlorocarbenium ions, including phenyldichlorocarbenium ions such as *(59)*, *(78)* and *(79)*[95–97, 116] and the perchlorotriphenylcarbenium ion *(80)*[117] *(Ballester)* have also been described. *West* observed the perchloroallyl cation *(81)*[118].

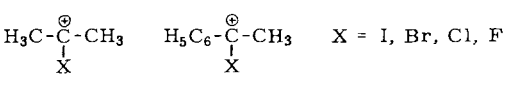


(59) (78) (79)



(80) (81)

Comisarow and *I* observed[119] a series of chloro-, as well as bromo- and iodocarbenium ions, and showed the general stabilizing ability of halogen attached to carbenium ion centers. [See also the fluoro compounds *(71)* and *(72)*.] *Halpern, Mo,* and *I* were subsequently able to study these effects in more detail using ^{13}C-NMR spectroscopy[120].



Closely related to the halocarbenium ions are the halonium ions in which the positive charge is to be found predominantly on the halogen atom. In our work with *Bollinger*[121] and *Peterson*[122], we reported on the three- and five-membered halonium ions of the type *(82)* and *(83)*.

(82) (83) (82a)

X = I, Br, Cl

R = H or Alkyl

Illustrative is the ^{1}H-NMR spectrum of propylenebromonium ion *(82a)* shown in Fig. 18.

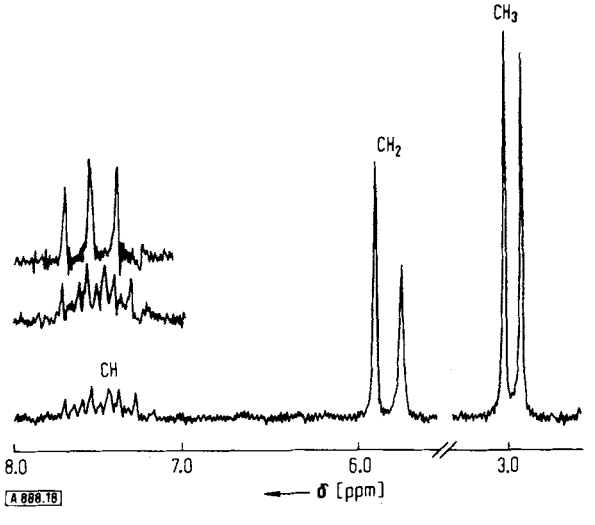


Fig. 18. ^{1}H-NMR spectrum (at 60 MHz) of the propylenebromonium ion *(82a)*. Left: Signal of the methine protons, decoupled.

In our work with *DeMember*[123] we were able to obtain not only ring halonium ions, but also a series of open-chain dialkylhalonium ions such as:

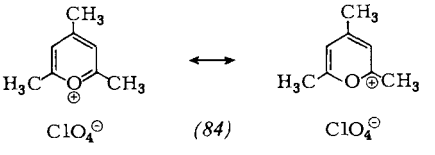
$[H_3C{-}I{-}CH_3]^{\oplus}$	$[[(CH_3)_2CH]_2Br]^{\oplus}$	$[H_3C{-}I{-}C_2H_5]^{\oplus}$
$[H_3C{-}Br{-}CH_3]^{\oplus}$	$[[(CH_3)_2CH]_2Cl]^{\oplus}$	$[H_3C{-}Br{-}C_2H_5]^{\oplus}$
$[H_3C{-}Cl{-}CH_3]^{\oplus}$	$[[(CH_3)_2CH]_2I]^{\oplus}$	$[H_3C{-}Cl{-}C_2H_5]^{\oplus}$
$[(C_2H_5)_2Br]^{\oplus}$	$[(n\text{-}C_3H_7)_2I]^{\oplus}$	$[CH_3{-}Cl{-}CH(CH_3)_2]^{\oplus}$
$[(C_2H_5)_2Cl]^{\oplus}$	$[(n\text{-}C_3H_7)_2Br]^{\oplus}$	
$[(C_2H_5)_2I]^{\oplus}$		

Dialkylhalonium fluoroantimonate salts can be isolated; they are versatile, very reactive alkylating agents, surpassing in many cases the selectivity and utility of *Meerwein*'s trialkyloxonium salts.

2.13. Oxygen as Heteroatom

Crystalline addition compounds of alcohols, ethers, aldehydes, and ketones with Brønsted and Lewis acids have been known since the middle of the last century. They were long considered as unstable "molecular compounds"[124]. *Collie* and *Tickle*[125] were the first (1899) to assign "oxonium salt" character to the acid complexes, *i.e.* they considered the compounds as containing a tetravalent oxygen, analogous to the ammonium salts in which nitrogen at that time was assumed to be pentavalent.

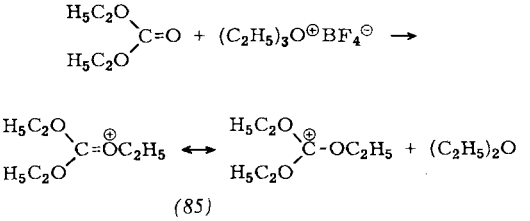
Hantzsch[126] proved, as early as 1922, that the pyrylium salts were clearly ionic. Pyrylium salts react with strong nucleophiles to give phenols. This behavior toward strong nucleophiles shows that the carbenium ion form contributes significantly to charge delocalization in pyrylium salts.



$ClO_4^{\ominus}$ (84) $ClO_4^{\ominus}$

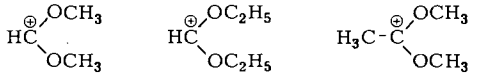
2.13.1. Alkoxy- and Hydroxycarbenium Ions

Resonance, similar to that in the pyrylium salts, was shown by *Meerwein*[127] to exist between tri- and dialkyloxonium and alkoxycarbenium ion forms in the fluoroborates obtained by alkylation of ketones, esters, and lactones with trimethyl- or triethyloxonium fluoroborates, such as *(85)*.



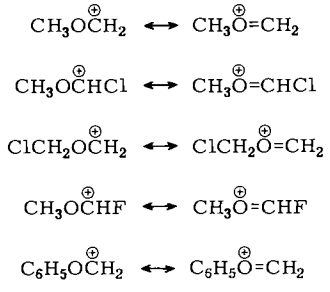
(85)

Taft and *Ramsey*[128] investigated a series of secondary and tertiary alkoxycarbenium ions *(86)*—*(88)* ^{1}H-NMR spectroscopically.



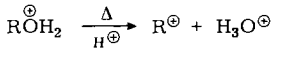
(86) *(87)* *(88)*

Bollinger[129] and *I* prepared primary alkoxycarbenium ions such as the methoxy- and phenoxycarbenium ions and their halogenated derivatives, and investigated their ^{1}H-, ^{13}C-, and later ^{17}O-NMR spectra.



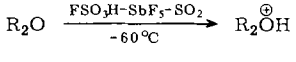
Acidic oxonium ion can be studied particularly well in superacid solvent systems. With *Sommer* and *Namanworth*[41] we showed that primary and secondary alcohols are protonated in FSO_3H—SbF_5(SO_2,SO_2ClF) solution at −60 °C, and that well-resolved NMR spectra of the protonated species can be obtained.

At higher temperatures they cleave to carbenium ions; the kinetics of these cleavage reactions could be followed by NMR spectroscopy.

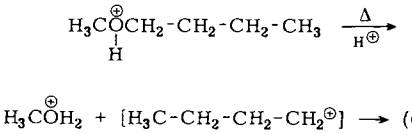


Tertiary alcohols (with the exception of the ones containing strongly electron-withdrawing groups like CF_3) generally dehydrate very fast in the acid media, and the intermediate protonated species cannot be observed, even at low temperature.

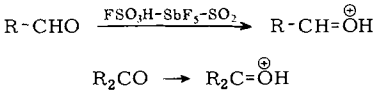
Ethers are also protonated in superacid media[43].



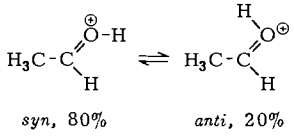
Once again the subsequent cleavage reactions can, as in the case of methyl *n*-butyl ether *(7)*, be followed by NMR spectroscopy.



Aldehydes and ketones are protonated on the carbonyl oxygen atom, and in superacid media at low temperatures the protonated species can be directly observed[130–134].

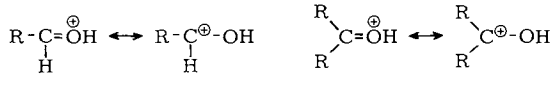


Even protonated formaldehyde has been prepared. Protonated acetaldehyde was observed in two isomeric forms, the proton on oxygen being *syn* or *anti* to the hydrogen of the aldehyde group.



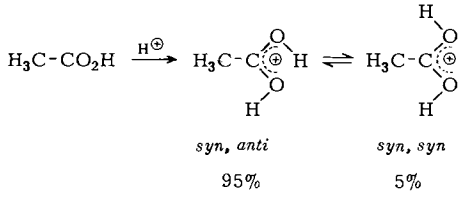
syn, 80% *anti*, 20%

The hydroxycarbenium ion forms of protonated ketones and aldehydes (obtained in strong acid solutions) contribute to the resonance hybrid, the degree of contribution of each form being quite accurately estimable by ^{13}C-NMR spectroscopy[135].



Carboxylic acids are protonated in superacid media such as FSO_3H—SbF_5—SO_2, HF—SbF_5, or HF—BF_3[136].

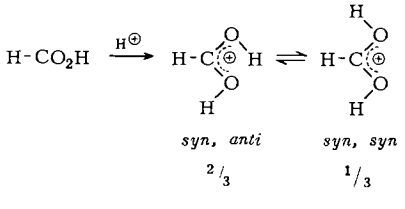
The NMR spectrum of acetic acid in such media at low temperatures shows two OH resonances. This indicates (i) that protonation of the carbonyl group is favored, and (ii) that rotation about the resultant C—OH bonds is hindered. The predominate conformer observed is the *syn,anti* isomer; but about 5 percent of the *syn,syn* isomer has also been observed.



syn, anti *syn, syn*

95% 5%

Formic acid is also protonated under the same conditions, two conformers being formed in the ratio 2:1; the *syn,anti* isomer predominates.

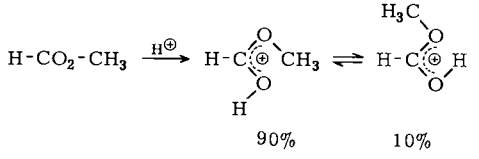


syn, anti *syn, syn*

$^2/_3$ $^1/_3$

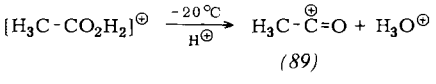
These isomers can be readily identified from the magnitudes of the vicinal coupling constants in the ^{1}H-NMR spectrum; thus in the *syn,anti* isomer, the methine proton gives a doublet of doublets (J_{HH} = 15 Hz and 3.5 Hz) while in the case of the *syn,syn* isomer a triplet is observed (J_{HH} = 3.5 Hz). No evidence for the *anti,anti* isomer has been found in either protonated carboxylic acids, esters, or their thio analogs.

Esters behave in an analogous fashion. Once again the oxygen atom of the carbonyl oxygen takes place. Thus, protonated methyl formate is present in FSO_3H—SbF_5—SO_2 solution as two isomers in a ratio of 90 to 10[137].



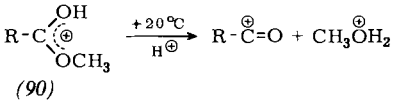
By raising the temperature of solutions of protonated carboxylic acids and esters, their cleavage reactions can be observed. These reactions can be considered within the framework of the two unimolecular reaction pathways for acid-catalyzed hydrolyses of esters, either involving alkyl- or acyl-oxygen cleavage. Studies of these reactions in superacid media have the advantage over those carried out under the usual solvolytic conditions in that the cleavage step can be isolated and studied in detail, since the cleavage products generally do not undergo further reaction.

For example, in the case of protonated acetic acid in FSO_3H—SbF_5—SO_2 solution, a reaction analogous to the rate-determining step in the unimolecular cleavage of esters is observed; this leads to formation of the acetyl cation *(89)* and the hydronium ion.

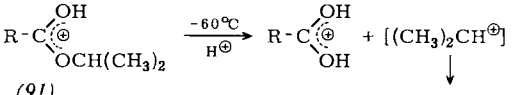


(89)

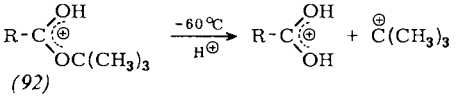
Unimolecular cleavage in this case corresponds to dehydration of the acid. In the case of protonated esters, however, the cleavage pathway depends on the nature of the alkoxy group, as is shown in examples *(90)*—*(92)*.



(90)

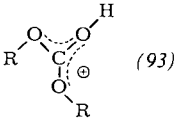


(91)



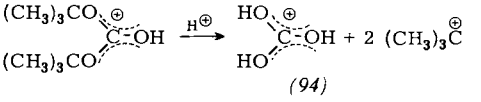
(92)

Dialkyl carbonates have been studied in FSO_3H—SbF_5 solution and have been shown to be protonated on the carbonyl oxygen giving the dialkoxyhydroxycarbenium ions *(93)*[138].



(93)

Di-*tert*-butyl carbonate cleaves spontaneously at −80 °C. Alkyl-oxygen fission takes place giving the *tert*-butyl cation and the protonated form of carbonic acid *(94)*, whose structure has been established from the ^{13}C-NMR spectrum (see Fig. 19). The quartet with a coupling constant of 4.5 Hz shows coupling of the carbon to three equivalent hydroxyl protons[138].



(94)

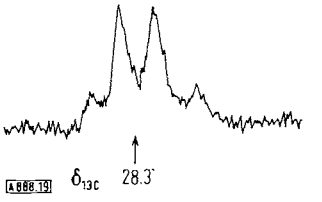
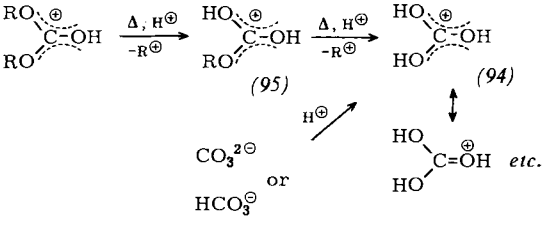
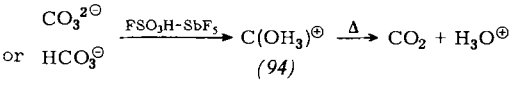


Fig. 19. ^{13}C-INDOR spectrum of the 56% ^{13}C-enriched protonated carbonic acid *(94)* (trihydroxycarbenium ion).

Di-isopropyl and diethyl carbonate cleave at a higher temperature, also *via* alkyl-oxygen cleavage, with initial formation of the protonated monoalkyl hydrogen carbonates *(95)*, which can also be obtained by protonation of their sodium salts. Upon further heating cleavage takes place to give protonated carbonic acid.



Protonated carbonic acid *(94)* can also be obtained by dissolving inorganic carbonates and hydrogen carbonates in FSO_3H—SbF_5 at −80 °C. It is stable in solution to about 0 °C, when it decomposes to the hydronium ion and carbon dioxide. Protonated carbon dioxide (CO_2H^+) may be an intermediate.



(94)

It is worthwhile to point out the close similarity between protonated carbonic acid *(94)* (the trihydroxycarbenium ion) and its nitrogen analog the guanidinium ion. Both are highly resonance stabilized through their onium forms.

The existence of protonated carbonic acid as a stable chemical entity with substantial resonance stabilization may have major implications in our understanding of some of the more fundamental biological carboxylation processes. Obviously the *in vitro* observation in specific, highly acidic, solvent systems cannot be simply extrapolated to different environments (biological systems). However, it is possible that on the active receptor sites of enzyme

systems (for example, those of the carbonic anhydrase type) local hydrogen ion concentration may be very high compared with the overall "biological pH". In addition, on the receptor sites a very favorable geometric configuration may help to stabilize the active species, a factor which cannot be reproduced in model systems *in vitro*.

2.13.2. Acyl Cations

In 1943 *Seel*[139] characterized the first stable acyl cation. Reaction of acetyl fluoride with boron trifluoride gave a complex (decomposition point 20 °C) which was characterized as the acetyl tetrafluoroborate salt.

$$H_3C{-}COF + BF_3 \rightleftharpoons H_3C{-}CO^{\oplus}BF_4^{\ominus}$$

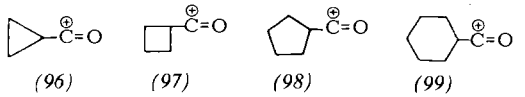
The identification was based on analytical data and chemical behavior. Only in the 1950's was further characterization of the complex by physical methods possible, namely by infrared and NMR spectroscopy. A series of acyl cations[140-142] (oxocarbenium ions) has been isolated and identified. The hexafluoroantimonate and hexafluoroarsenate complexes were found to be particularly stable[142]. *Deno et al.* investigated solutions of carboxylic acids in sulfuric acid and oleum[143]. They observed protonation at lower acid concentrations, and dehydration to give acyl cations at higher acidities.

$$R{-}CO_2H \xrightleftharpoons{H_2SO_4} R{-}\overset{\oplus}{C}O_2H_2 \xrightleftharpoons{\text{Oleum}} R{-}\overset{\oplus}{C}{=}O + H_3O^{\oplus}$$

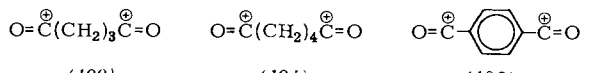
The investigation of acyl cations like the acetyl, propionyl, butyryl, isobutyryl, pivaloyl and benzoyl cation was substantially helped by NMR studies. Not only ^1H, but also ^2H, ^{13}C, and ^{19}F resonance studies established the structure of these ions[142,144]. The ^{13}C- and ^1H-NMR spectra showed that in the case of acyl cations, such as the acetyl cation *(89)*, a resonance hybrid of the oxonium ion, oxocarbenium ion, and of the ketene-like form is involved.

$$H_3C{-}C{\equiv}O^{\oplus} \longleftrightarrow H_3C{-}\overset{\oplus}{C}{=}O \longleftrightarrow \underset{H^{\oplus}}{CH_2{=}C{=}O}$$

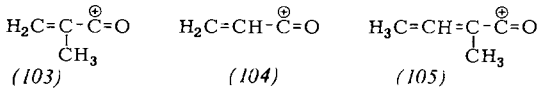
Recent x-ray crystallography studies of the $CH_3CO^+{-}SbF_6^-$ complex substantiated this suggestion and provided convincing evidence for the linear structure of the crystalline complex[145].



(96) *(97)* *(98)* *(99)*



(100) *(101)* *(102)*

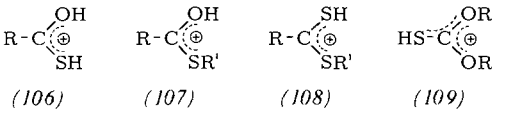


(103) *(104)* *(105)*

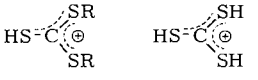
Investigation of acyl cations has been extended to the study of acyl cation, *i.e.* cycloacyl cations such as *(96)* to *(99)*[146], unsaturated acyl cations such as *(103)* to *(105)*[147], and diacyl cations such as *(100)*—*(102)*[148].

2.14. Sulfur as Heteroatom

Thiols and sulfides are protonated on sulfur and give, in superacid media, the stable mono- and dialkylsulfonium ions respectively[47]. Thiocarboxylic acids, *O*- and *S*-alkyl thioesters, dithioesters, and thiocarbonates also form stable thiohydroxy or thioalkoxycarbenium ions[158]. Examples are the ions *(106)*—*(111)*.



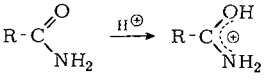
(106) *(107)* *(108)* *(109)*



(110) *(111)*

2.15. Nitrogen as Heteroatom

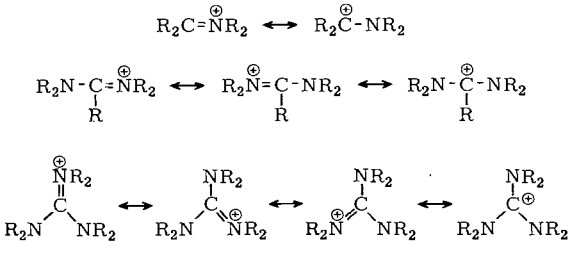
Amides are protonated in superacid media at low temperatures on the carbonyl oxygen atom, as was first shown by *Gillespie*[149].



It has been claimed[150] that protonation of ethyl *N,N*-diisopropylcarbamate, a hindered amide, takes place on nitrogen and not on oxygen. A reinvestigation, however, established that at low temperature *O*-protonation first takes place (kinetic control) and that the *O*-protonated amide subsequently rearranges to the more stable *N*-protonated form (thermodynamic control)[151].

The possibility of observing the protonated amide linkage in strong acid media has particular relevance in the study of peptides and proteins[152,153].

Since nitrogen is a much stronger electron donor than oxygen, the contribution of carbenium ion structures in acid salts of imines, amidines, and guanidines is small[154].



However, even in protonated nitriles contribution from the iminocarbenium ion resonance form must also be considered[155,156].

$H_5C_2-C\equiv\overset{\oplus}{N}H \leftrightarrow H_5C_2-\overset{\oplus}{C}=NH$

Ions such as the triazocarbenium ion, $(N_3)_3C^+SbCl_6^-$, have also been reported[157].

The field of protonated heteroaliphatic compounds has been studied in detail; interested readers are referred to a recent review[158] for more information.

3. Equilibrating Carbenium Ions or Static Carbonium Ions? The Classical-Nonclassical Ion Controversy

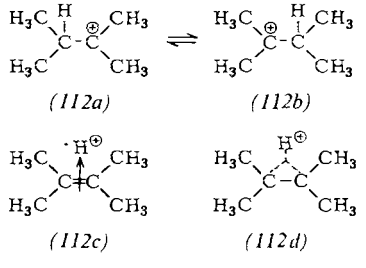
Some carbocations show great tendency to undergo fast degenerate rearrangements, leading through intramolecular hydrogen or alkyl shifts to the related identical structures[2]. The question arises, whether these processes are equilibrations between the limiting carbenium ("classical") ion intermediates separated by low energy level transition states or whether intermediate hydrogen or alkyl bridged carbonium ions are involved. Extensive discussions regarding the kinetic and stereochemical results in these systems have already appeared in the literature and it is considered outside the scope of this review to recapitulate the arguments. The reader is referred to reviews, such as *Schleyer*'s[2], and the original literature.

As direct observation of long-lived carbocations, generally in superacid media, became possible in recent years it was as a logical extension of our work to apply the developed spectroscopic and chemical studies of direct observation to the study of equilibrating or bridged carbocation systems. Differentiation between these two possibilities by NMR spectroscopy is difficult; because of the "slow time scale" of the NMR method, rapidly equilibrating or bridged ions can be expected to give similar ^{1}H-NMR spectra.

^{13}C-NMR spectra can, however, be used advantageously[30] for investigation of the structure of carbocations in which the possibility exists for degenerate rearrangements to occur which are fast with respect to the NMR time-scale and which lead to average shifts and coupling constants being observed. "Rapid" methods such as IR, Raman, and especially ESCA spectroscopy are therefore particularly useful for investigating these systems.

3.1. Equilibrating Alkylcarbenium Ions

The dimethylisopropylcarbenium ion is an example of a rapidly equilibrating alkylcarbenium ion. Its ^{1}H-NMR spectrum, shows four equivalent methyl groups and does not permit a clear distinction to be made between a rapidly equilibrating system or a static ion [which may be formulated as involving hydrogen bridging, *i.e.* a π-complex *(112c)* or alkenonium ion *(112d)*].



(112a) ⇌ *(112b)*

(112c) *(112d)*

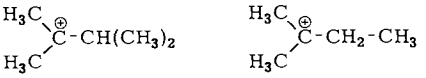
The average ^{13}C chemical shift observed for the two central carbons of the dimethylisopropylcarbenium ion is $\delta = 3.4$. The INDOR spectrum consists of a, doublet ($J_{CH} = 65$ Hz)[27]. In the case of an equilibrating system the average value of the shifts at the two sites, *i.e.* C^+ and $HC<$, would be observed as the chemical shift. A suitable model for estimating these shifts is the *tert*-butyl cation; the average value of the ^{13}C chemical shift of the methyl group and of the central C^+ atom is $\delta_{^{13}C} = 6.2$. The effect of the two additional methyl groups in *(112)* should cause additional deshielding of both shifts compared with those in the model compound, and thus there is excellent agreement between the observed shift and the chemical shift expected for the rapidly equilibrating ion. The coupling constant can also be estimated (again using the *tert*-butyl cation as a model compound) from the direct and long-range C—H coupling constants J_{HC} and J_{HCC}. The average of these values (assuming the long-range coupling to be negative, as is usual in three-bond CCH coupling) is 64 Hz, again in excellent agreement with the observed value. The agreement of both the coupling constants and the chemical shift with the values predicted for the rapidly equilibrating ion are so good as to leave little doubt as to the nature of this ion. IR and Laser Raman spectroscopic studies of the ion also confirm this conclusion. Whereas NMR studies of rapidly equilibrating ions are thus possible, clearly the relatively slow time-scale of the NMR experiment does not allow direct, separate observation of individual species, but gives information through analysis of *average* chemical shifts and coupling constants of the equilibrating species. Thus it is clear that the study of these ions necessitates the use of physical methods whose time scale is not affected by even the fastest chemical equilibrating processes.

Consequently we carried out a study of the infrared and Raman spectra[25, 32] of the isopropyldimethylcarbenium ion and, for comparisons, those of a series of alkylcarbenium ions with known "static" structure, such as the *tert*-butyl, *tert*-amyl, and isopropyl cations. The nearly identical spectra of the ions and the evident planarity (or near planarity) of the carbenium centers suggest that the dimethylisopropylcarbenium ion is "classical", similarly to the static ions used for comparison.

Finally, the most decisive physical method yet applied to the study of carbocations in the condensed state is perhaps that of x-ray photoelectron spectroscopy (ESCA)[36], which allows one to differentiate between equilibrating carbenium ions and bridged carbonium ions. This method allows direct measurement of carbon 1s electron binding energies. As the charge distribution within carbocations causes increasing binding energies with increasing positive charge localization, highly electron deficient classical alkyl and cycloalkyl carbenium centers (as in *tert*-butyl and *tert*-amyl cations) show at least 4 eV binding energy differences from the remaining less electropositive carbon atoms.

In the ESCA spectra of bridged carbonium ions, such as the norbornyl cation (see Section 3.3), there is no indication

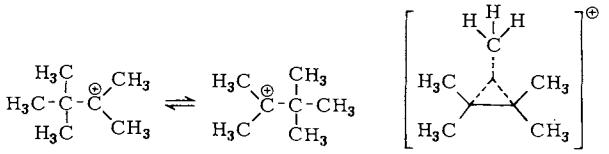
of such a highly electron deficient carbon center with high binding energy. The ESCA spectra of the dimethylisopropylcarbenium ion *(112)* and of the dimethylethylcarbenium ion *(113)* show practically the same difference in the 1s bonding energies (ΔE_b) between C^+ and adjacent C atoms ($\approx$4.2eV).



(112) *(113)*

Since ESCA spectra represent observation of the ejected core electron from a single species, no time scale limitation related to possible chemical equilibration phenomena can exist. The ESCA spectra thus clearly indicate that the ion studied is a classical carbenium ion and not a bridged tetramethylethyleneprotonium ion *(112d)*.

An example for differentiating between an equilibrating and a methyl bridged ion is the dimethyl-*tert*-butylcarbenium ion *(114)* (the triptyl cation or pentamethylethyl cation). The ^{1}H-NMR spectrum of this ion consists of a single signal at $\delta = 2.90$[45]. The position of this chemical shift was considered indicative of a rapidly equilibrating structure [*(114a)*$\rightleftharpoons$*(114b)*] rather than a bridged structure *(114c)*, although the fact that only a single proton

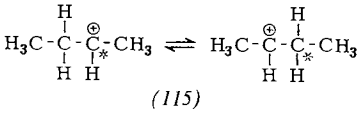


(114a) *(114b)* *(114c)*

resonance is observed does not necessarily enable these structures to be distinguished since in the methyl bridged carbonium ion intramolecular equilibration of the methyl groups could take place. As in the case of the dimethylisopropylcarbenium ion the ^{13}C-NMR spectral data can give additional evidence about the structure[30].

The average ^{13}C chemical shift for C-2 and C-3 was found to be $\delta_{^{13}C} = -11.5$; this is consistent only with the rapidly equilibrating structure. The norbornyl cation (see Section 3.3), which has been experimentally observed, provides a good model for a methyl bridged ion. The bridged carbon atoms in this ion have a chemical shift $\delta_{^{13}C} = 70$. If the dimethyl-*tert*-butylcarbenium ion is similar in nature to the norbornyl cation we would expect the C-2 and C-3 shifts in the former compound to be 81.5ppm further upfield than they actually are. The near zero coupling between the methyl protons and carbon-13 is also revealing. Since this ion rapidly equilibrates, the observed coupling will be the average of the two and three bond carbon-hydrogen coupling constants. The two bond coupling constant in the *tert*-butyl cation is 6.5 Hz. A similar value is to be expected for the methyl bridged ion. Since the observed coupling constant is zero, the three bond coupling must have the same magnitude but opposite sign. So far the signs of only a few such couplings have been determined. However, such a sign alternation has been reported by *Karabatsos*[31a], the two bond coupling being negative and the three bond coupling positive.

The ^{1}H-NMR spectrum of the 2-butyl cation *(115)* at -120 °C consists of two signals at $\delta = 3.2$ and 6.7, the



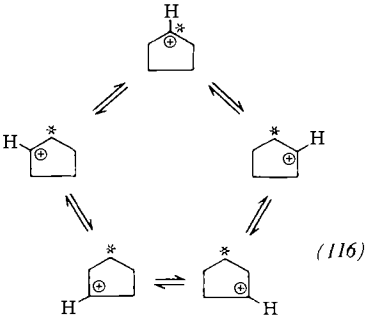
(115)

intensity ratio being 2:1[159]. This is the result of a degenerate 1,2 hydrogen shift, which at this temperature is fast with respect to the NMR time-scale.

In the ^{13}C-NMR spectrum the two central carbons give a quartet at $\delta_{^{13}C} = 21.2$ with a carbon-hydrogen coupling constant of $J_{CH} = 70 \pm 2$ Hz[30]. Using the difference of the ^{13}C shifts observed in the dimethylisopropyl ion *(112)* and the dimethyl-*tert*-butylcarbenium ion *(114)* as a measure of the effect of methyl substitution on the ^{13}C chemical shift in equilibrating ions (8 ppm) then a ^{13}C chemical shift of $\delta_{^{13}C} = 13$ is to be expected. This is in reasonable agreement with the observed value. Using the isopropyl cation as a model gives an estimated coupling constant of 72 Hz. As in the two previous examples the ^{13}C-NMR values clearly demonstrate that the 2-butyl cation is an equilibrating "classical" carbenium ion rather than a bridged "non-classical" carbonium ion. Both Raman and ESCA spectroscopic studies of the pentamethylethyl and 2-butyl cations clearly indicate the classical carbenium ion nature of the ions. The 1s binding energies of the carbenium centers and the remaining carbon atoms differ in the case of the tertiary ions by about 4.0—4.8 $\pm$ 0.2 eV.

3.2. The Equilibrating Cyclopentyl Cation

As already mentioned the ^{1}H-NMR spectrum of the cyclopentyl cation *(116)* in SbF_5—SO_2ClF solution at -70 °C consists of a singlet at $\delta = 4.68$. The ^{13}C satellites of this



(116)

peak show a J_{CH} coupling constant of 28.5 Hz and have an intensity five times that normally observed. This results from the degenerate rearrangements that occur in this ion which, on the NMR time-scale, lead to equivalence of the nine protons and five carbon atoms. The ^{13}C-

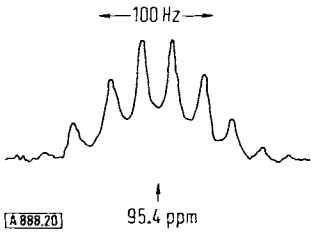


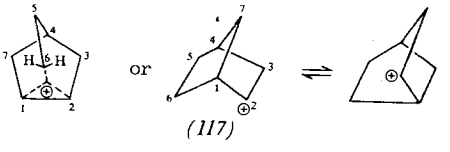
Fig. 20. 25 MHz ^{13}C-INDOR spectrum of the cyclopentyl cation obtained in natural abundance from cyclopentyl chloride in SO_2ClF—SbF_5 solution. The ten-line multiplet (J_{CH} = 28.5 Hz) is a result of the degenerate rearrangements in this ion leading to complete scrambling of the nine protons among the five carbons on the NMR time scale. The observed shift and coupling constant are thus average values.

INDOR spectrum shows a 10 line multiplet at $\delta_{^{13}C} = 95.4$ with a coupling constant of 28.5 Hz[30] (Fig. 20).

Once again the ESCA spectrum[36], which is not affected by the time scale of equilibration, shows that the ion *(116)* is a secondary carbenium ion. The binding energies of the carbenium carbon atom and remaining carbon atoms differ by about 4.8 eV.

3.3. The Norbornyl Cation

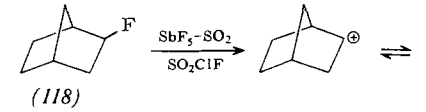
The cyclopentyl cation *(116)* leads us to the discussion of one of the most controversial of all carbocations, the



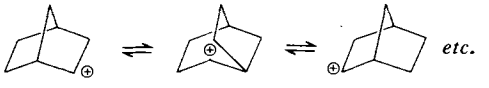
(117)

norbornyl cation *(117)*, whose structure has been the central point of many discussions regarding the much publicized classical-nonclassical controversy of "carbonium ions"[9].

The methods worked out in our laboratories to generate and study stable carbocations in solution were successfully applied to the direct observation of the norbornyl cation and the clarification of its structure[10].



(118)



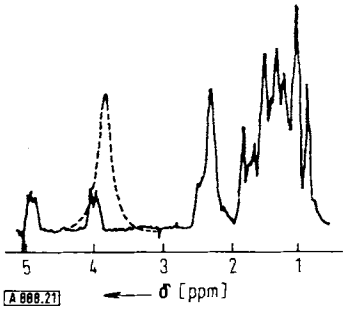


Fig. 21. 60-MHz ^{1}H-NMR spectrum of the norbornyl cation *(117)* (- - -) and the 2-*exo*-fluoronorbornane *(118)* (——) at 35 °C.

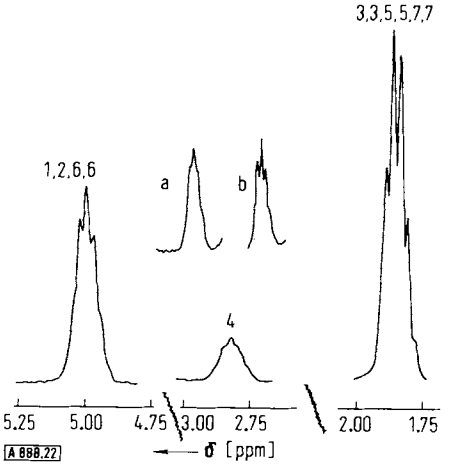


Fig. 22. ^{1}H-NMR spectrum (100 MHz) of the norbornyl cation *(117)* in SbF_5—SO_2 solution at −80 °C. The insert shows the effect of irradiating the low-field septuplet on the one-proton peak at δ = 2.82. a is the spectrum without irradiation and b is with irradiation.

In 1964 *Saunders, Schleyer,* and *I* first investigated[160] the ion prepared from 2-*exo*-fluoronorbornane *(118)* in SbF_5—SO_2 and recorded its ^{1}H-NMR spectrum. At room temperature it consists of a single broad band at δ = 3.75 (Fig. 21) due to scrambling of all hydrogen atoms. The contrast between this single band and the complex spectrum of the starting compound is striking. The equilibration of the hydrogen atoms is caused by the fast 3,2- and 6,2-hydrogen shifts and the Wagner-Meerwein rearrangement.

Similarly at room temperature the ^{13}C-NMR spectrum of the ion shows a single broad absorption line centered at $\delta_{^{13}C} = 134$[10].

When the temperature is lowered to −60 °C the ^{1}H-NMR spectrum of the 2-norbornyl cation is resolved into three different peaks (intensity ratio 4:1:6). The spectrum does not change when the temperature is lowered to −120 °C[10] (Fig. 22).

The spectrum was interpreted as evidence that the 3,2-hydrogen shift could be frozen out, but the 6,2-hydrogen shift and the Wagner-Meerwein rearrangement are still fast even at the low temperatures used (−120 °C). The rate constant of the slow 3,2-hydrogen shift was established from temperature-dependence studies, and the activation energy of this shift was found to be 12 kcal/mol. In studies with *White*[10] we subsequently succeeded in "freezing out" on the NMR time scale even the fast 6,2-hydrogen shift. Using a mixed solvent system (SbF_5—SO_2ClF—SO_2F_2) it was possible to observe the 100 MHz spectrum at temperatures down to −156 °C. At −120 °C, the spectrum was identical to that described previously; however, in the temperature range −128 to −150 °C significant changes occur. The most deshielded peak due to the four equilibrating "protonated cyclopropane" ring protons broadens and then separates into two signals at δ = 3.05 and 6.59 with relative intensities 2:2. The high field resonance, due to the six methylene protons, also broadens and develops a shoulder at δ = 1.70. The signal at δ = 2.82 due to the single bridgehead proton remains unchanged (Fig. 23).

The temperature dependence of the low field resonance was used to calculate the rate constants based on the

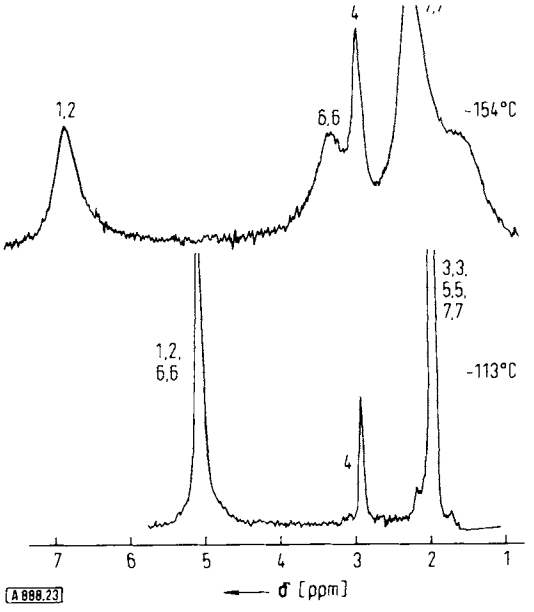


Fig. 23. 100-MHz ^{1}H-NMR spectrum of the "norbornyl cation" in SbF_5—SO_2ClF—SO_2F_2 solution at temperatures between −113 and −154 °C.

Gutowsky-Holm equations. The activation energy from the Arrhenius plot is 5.9 ± 0.2 kcal/mol^{-1} and the pre-exponential factor $10^{12.7}$ s^{-1}.

These observations could signify either: (a) that the ion is "classical" and that the temperature dependence corresponds to the "freezing out" of the 6,1,2-hydrogen shift, the Wagner-Meerwein rearrangement still being fast at −156 °C, or (b) that the ion is "non-classical", all rearrangements have been "frozen out" and thus the structure is that of a methylene bridged ion with a pentacoordinated carbon atom.

In order to differentiate between these two possibilities the Raman and ^{13}C-NMR spectra of the ion were studied[10]. As Raman spectroscopy is a rapid physical method (assuming that vibrational transition rates are faster than any of the hydrogen or alkyl shifts) the question of possible equilibration *versus* bridged ion becomes unimportant. The previously discussed technique of average ^{13}C-NMR shifts should be also applicable in this case for differentiating a static nonclassical bridged ion from rapidly equilibrating classical carbenium ions.

The Raman spectroscopic investigation of the stable norbornyl cation was carried out at −70 °C in FSO_3H—SbF_5—SO_2 solution using a helium-neon laser. In the C—C stretching frequency region there is only one strong line at 972 cm^{-1} ($\rho = 0.35$). The C—H stretching frequency region shows five lines, one of which is at 3110 cm^{-1}. The skeletal vibrations of the ion and their comparison with those of model compounds suggest a structure closer related to nortricyclene, but not to norbornane, *i.e.* under the conditions of the investigations (−70 °C, where, as the NMR spectra show, the ion rapidly equilibrates) an ion having protonated nortricyclene nature is present.

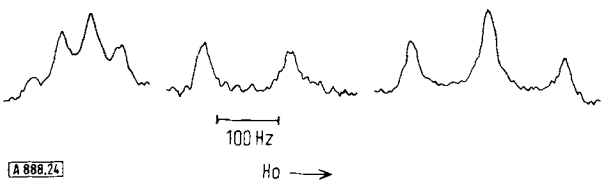


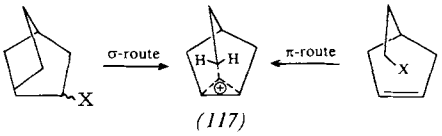
Fig. 24. ^{13}C-INDOR spectrum of the norbornyl cation *(117)* generated in SbF_5—SO_2 solution from *exo*-2-chloronorbornane and recorded at −70 °C. The spectrum was obtained by observing the ^{13}C satellites in the 100-MHz ^{1}H-NMR spectrum while irradiating the sample with a swept 25-MHz frequency. ^{13}C shifts indicated are with respect to $^{13}CS_2$.

As mentioned, the ^{13}C-NMR spectrum of the ion at room temperature shows a single broad absorption. On lowering the temperature to −70 °C, three well resolved absorptions are observed (Fig. 24). The chemical shift of the triplet due to the equivalent methylene carbon atoms C-3, C-5 and C-7 is at $\delta_{^{13}C} = 162.5$ ($J = 140.2$ Hz) and that of the bridgehead carbon atom C-4 at $\delta_{^{13}C} = 156.1$ (doublet $J = 153$ Hz). The 53.3 Hz pentuplet observed at $\delta_{^{13}C} = 101.8$ (from $^{13}CS_2$) using the INDOR method (on irradiation of the satellites of the lowest field peak) corresponds to the three equivalent carbons C-1, C-2 and C-6 associated with the four equivalent equilibrating protons.

Subsequently we were also able to obtain the ^{13}C-NMR spectrum of the "frozen out" norbornyl cation at −156 °C. Whereas the use of the INDOR method is generally based on observing the effects of irradiation on the ^{13}C satellites in the proton spectrum, these satellites could not be observed at −156 °C due to a poor signal-to-noise ratio at this very low temperature. Enhancement of the C-1, C-2-proton resonance (due to a collapse of the ^{13}C satellites and possibly a nuclear Overhauser effect) proved to be possible on irradiation at 25.1 MHz, however, even at −156 °C. The low-field proton resonance (at $\delta = 6.59$) was enhanced on irradiation at $\delta_{^{13}C} = 70 \pm 2$ while the more shielded proton resonance (at $\delta = 3.05$) was enhanced on irradiation at a frequency corresponding to $\delta_{^{13}C} = 173 \pm 2$.

We were unable to obtain the C—H coupling constants and peak multiplicities in this manner. Recently, however, it has been possible by use of the rapid Fourier Transformation Method to obtain the complete ^{13}C-NMR spectrum, and all the coupling constants and peak multiplicities. Table 3 lists the corresponding values of the carbon atoms participating in the three center bond.

It should also be mentioned that both the "σ-route" from 2-norbornyl halides and the "π-route" from β-Δ^3-cyclopentenylethyl halides lead to the same norbornyl cation *(117)*.



(117)

Recently *Mateescu, Riemenschneider*[36], and *I* succeeded in recording the ESCA spectrum of the norbornyl cation and compared it with that of the 2-methylnorbornyl cation and other trivalent carbenium ions, such as the cyclopentyl

and methylcyclopentyl cations *(116)* and *(37)*. The 1s electron spectrum (Fig. 25) of the norbornyl cation *(117)* shows no high binding energy carbenium center and a maximum separation of less then 1.5 eV between the two "cyclopropyl" type carbons, to which bridging takes place, from the other carbon atoms (including the pentacoordinated bridging carbon). In contrast the 2-methylnorbornyl cation shows, like other trivalent carbenium ions, a high binding energy carbenium center that is only slightly delocalized, as indicated by the binding energy difference of 3.7 eV from the other carbon atoms.

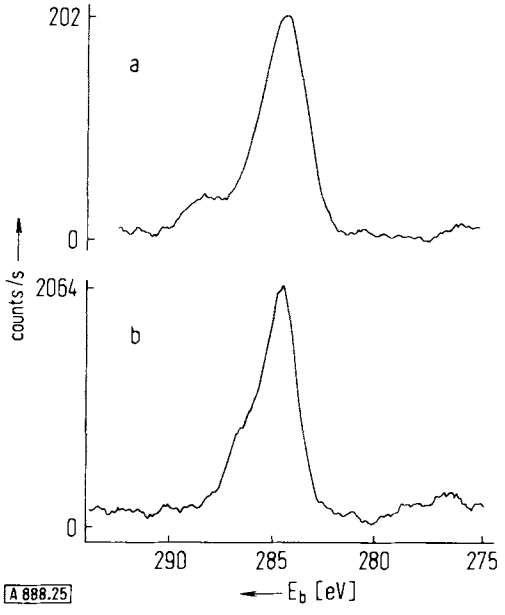


Fig. 25. Carbon 1 s electron spectrum (ESCA spectrum) a) of the 2-methylnorbornyl cation and b) of the norbornyl cation *(117)*. E_b = binding energy.

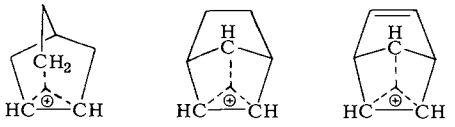
Since in electron spectroscopy the time scale of the measured ionization processes is of the order of 10^{-16} s, definite ionic species can be characterized, regardless of possible intra- and intermolecular interactions (*e.g.* Wagner-Meerwein rearrangements, hydrogen shifts, proton exchange, *etc.*), which have no effect. Thus, ESCA spectroscopy gives an undisputable, direct answer to the long debated question of the "nonclassical" nature of the norbornyl cation independent of any possible equilibration process.

The bridging methylene carbon atom C-6 of the norbornyl ion is pentacoordinated. It is bound to two hydrogen atoms and to the carbon atom C-5 by three two-electron single bonds. The remaining sp^3 orbital is involved in two-electron three-center bonding with C-1 and C-2. Thus the pentacoordinated carbonium ion center is similar to CH_5^+ and the norbornyl ion is a carbonium ion.

Other examples of directly observed long-lived carbonium ions in which pentacoordinated carbonium centers were identified by ^{13}C and ^1H-NMR spectroscopy are the 7-norbornenyl *(119)* and the 7-norbornadienyl cation *(120)*[10,161].

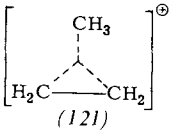
Winstein[162] and *Richey*[163] have shown that the 7-norbornenyl cation *(119)* can be obtained *via* both the "σ-route" and the "π-route".

The carbonium centers in the norbornyl cation *(117)*, the 7-norbornenyl cation *(119)*, and the 7-norbornadienyl cation *(120)*[10,164] are similar and related to the ethylene-



(117) *(119)* *(120)*

methonium ion *(121)*, although strain differences in the ions are obviously significant. All these ions contain a two electron three-center bond. The bridging carbon atoms are pentacoordinated, whereas the carbons to which they bridge are tetracoordinated carbonium atoms.



(121)

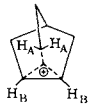
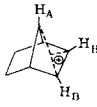
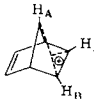
Comparison of the characteristic ^{13}C-NMR parameters of the carbonium centers in these ions with those of trivalent carbenium centers in related tertiary classical ions (Table 3) shows the very significant differences which allow clear differentiation. The carbenium centers are highly electron deficient and therefore deshielded, whereas the carbonium centers show much higher shielding (up to 300 ppm) on account of their higher coordination.

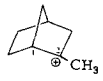
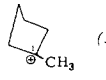
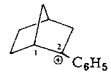
It can be concluded that the original views of *Winstein*[165] on the nonclassical nature of the norbornyl cation, based on kinetic and stereochemical results, have been fully substantiated by direct spectroscopic studies of the long-lived ion[10]. Whether the ion is completely formed under solvolytic conditions (S_N1 type) or the reaction has more S_N2 character, cannot be decided at the present time. Investigation of the norbornyl cation, however, contributed substantially to our general understanding of carbonium ions as being distinct and well differentiated species from carbenium ions. Carbonium ions cannot only be formed intramolecularly, but also in intermolecular reactions and represent the key for electrophilic reactions on single bonds (see following discussion).

3.4. Cyclopropylmethyl and Cyclobutyl Cations

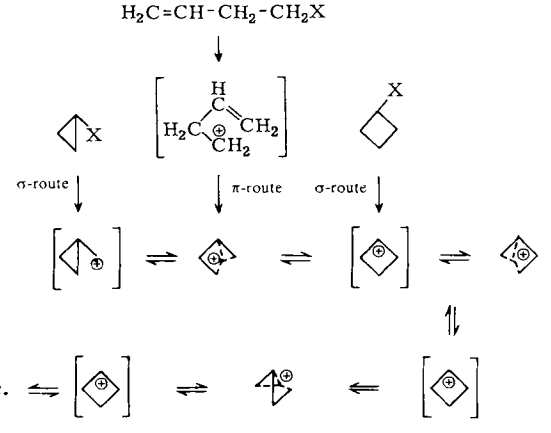
The solvolytic reactions of the cyclopropylmethyl—cyclobutyl—allylmethyl system has been studied extensively by *Roberts*[166], *Wiberg*[167], and other authors. In these studies and in recent spectroscopic investigations of the long-lived ions in superacids[76], the nonclassical nature of the common ions could be established. Rapid equilibration between the so-called unsymmetrical bicyclobutonium ions is in agreement with all data.

Table 3. Comparison of the ^{13}C-NMR parameters of the carbocation centers in carbonium and carbenium ions.

Ion	Carbonium ions δ[ppm]	J_{CH}[Hz]	$\delta_{^{13}C}$[ppm]
 *(117)*	$H_A = 3.05$ $H_B = 6.59$	$H_A = 145.8$ $H_B = 184.5$	$C_A = 171.4$ $C_B = 68.5$
 *(119)*	$H_A = 3.25$ $H_B = 7.04$	$H_A = 218.9$ $H_B = 193.8$	$C_A = 159.8$ $C_B = 67.9$
 *(120)*	$H_A = 3.24$ $H_B = 7.48$	$H_A = 216.4$ $H_B = 192.3$	$C_A = 157.6$ $C_B = 78.9$

Ion	Carbenium ions Solvent T[°C]	$\delta_{^{13}C}$[ppm]
	$FSO_3H—SbF_5—SO_2$ −80	C-1 = +113.0 (J = 169.5 Hz) $C^{\oplus}$-2 = −77.3
 *(37)*	$SbF_5—SO_2$ −60	$C^{\oplus}$-1 = −142.0
$(CH_3)_3C^{\oplus}$ *(2)*	$SbF_5—SO_2ClF$ −60	$C^{\oplus}$ = −135.4
$(CH_3)_2CH^{\oplus}$ *(1)*	$SbF_5—SO_2ClF$ −60	$C^{\oplus}$ = −125.0
	FSO_3H −35	C-1 = +134.0 (J = 158.4 Hz) $C^{\oplus}$-2 = −63.5
	FSO_3H −20	$C^{\oplus}$-1 = −74.6
$(CH_3)_2\overset{\oplus}{C}C_6H_5$ *(42)*	$FSO_3H—SbF_5—SO_2$ −60	$C^{\oplus}$ = −61.1

Stable, long-lived cyclopropylmethyl and cyclobutyl cations were studied in $SbF_5—SO_2ClF$ solution at low temperature by ^{1}H- and ^{13}C-NMR spectroscopy. Structural assignments were based on the data obtained and on comparison with model compounds. The cyclopropylmethyl cation *(122)* (Fig. 26) and for comparison the



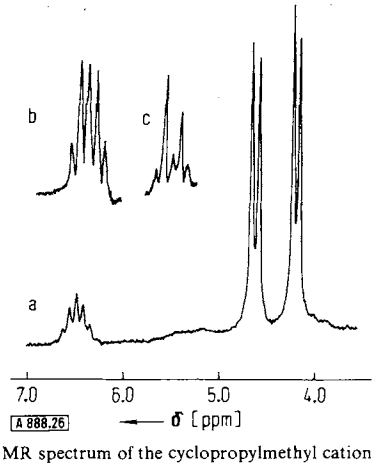
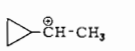
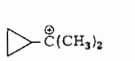


Fig. 26. a) 100-MHz ^{1}H-NMR spectrum of the cyclopropylmethyl cation *(122)* in $SbF_5—SO_2ClF$ solution at −80 °C. b) 60-MHz spectrum in the region of the CH signal; c) 60-MHz spectrum the CH signal of the α,α-dideuteriocyclopropylmethyl cation.

methyl substituted cations *(123)* and *(14)* were examined under comparable conditions. The NMR parameters are summarized in Table 4.

Table 4. NMR parameters of cyclopropylmethyl cations.

Ion	CH_3	^{1}H-NMR, δ [ppm] (J_{H-H} [Hz]) CH_2	CH	$^{\oplus}$CH
(122)		4.21 (6.5) 4.64 (8.0)	6.50 (6.5, 8.0)	
 *(123)*	3.34 (6.2)	4.32 4.45	4.58	9.6 (6.2)
 *(14)* [a]	2.70 3.18 (1.25)	3.57 3.68	3.83	

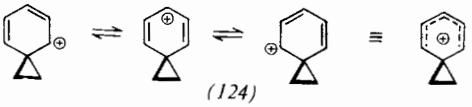
Ion	^{13}C-NMR, δ [ppm] ($J_{^{13}CH}$ [Hz]) CH_3	CH_2	CH	$C^{\oplus}$
(122)		+138 (180)	+ 85	
(123)	+160	+136	+126	−59.1
(14)	+154 (125) +163 (125)	+140	+134	−86.8

[a] See also Fig. 7.

All of the cyclopropylmethyl cations show charge delocalization by the cyclopropyl ring, but only with the primary system is the unique behavior observed which puts it in a class distinct from the secondary and tertiary ions. Comparison with model compounds, including the previously discussed norbornyl type cations, established the nonclassical carbonium ion nature of the cyclopropylmethyl cation *(122)*. A set of equilibrating cyclopropylcarbonium ions is involved, with equilibration occurring *via* the puckered cyclobutenium ion (cyclobutyl cation).

3.5. Ethylenearenium Ions

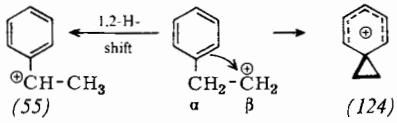
The classical-nonclassical ion controversy also included the question of the so-called "ethylenephenonium" ions. *Cram*'s extensive studies[168], based on kinetic and stereochemical evidence, clearly established the bridged-ion nature of β-phenylethyl cations in solvolytic systems. Spectroscopic studies (particularly ^{1}H- and ^{13}C-NMR)[169] of a series of stable long-lived ions proved the symmetrically bridged structure, and at the same time showed that these ions do *not* contain a pentacoordinated carbonium ion center (*i.e.* they are not "nonclassical ions"). They are spiro[2.5]octadienyl cations *(124)* (spirocyclopropylbenzenium ions) or, in other words, cyclopropylmethyl cations in which the carbenium center belongs to a cyclohexadienyl cation (benzenium ion).



(124)

The nature of the spiro carbon atom is of particular importance in determining the structure of these carbocations. ^{13}C-NMR spectroscopic studies clearly established the aliphatic tetrahedral nature of this carbon, thus ruling out a "nonclassical" ethylenephenonium ion.

The formation of the ethylenebenzenium ion *(124)* from β-phenylethyl precursors can be depicted as cycloalkylation of the aromatic π-system and not, as such, of the C_{Ar}—C_α bond which would give the tetracoordinated ethylenephenonium ion. Rearrangement of the β-phenylethyl to α-phenylethyl cations on the other hand is a regular 1,2-hydrogen shift involving the C_α—H bond.



(55) *(124)*

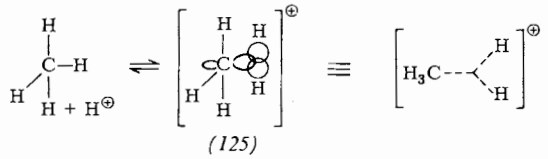
4. The Role of Carbocations in Electrophilic Reactions

4.1. General Considerations

Trivalent carbenium ions, as recognized in the pioneering work of *Meerwein*, *Ingold*, and *Whitmore*, play an important role in acid-catalyzed rearrangements of hydrocarbons (isomerization, alkylation, cyclization, polymerization, *etc.*), as well in a large variety of electrophilic reactions including those of the generalized Friedel-Crafts type. These reactions and their mechanisms are well reviewed[170] and will not be discussed here. It is suggested, however, (see subsequent discussion) that only ionization of lone (non-bonding) electron pair donor precursors (n-bases) or protonation of singlet carbenes can lead directly to carbenium ions. Other (π- or σ-) donors always interact first *via* their bonding electron pairs with the electrophilic reagents, forming two electron three-center bound carbonium ions (transition states or intermediates) which subsequently yield the trivalent carbenium ions.

4.2. Formation of Methonium Ion (the Simplest Carbonium Ion) from Methane

The bonding of a carbonium center is considered to involve three covalent, two-electron bonds with the fourth bond being a two-electron three-center bond[12]. This type of bond occurs, similarly as in the norbornyl cation *(177)*[10], in alkonium ions like CH_5^+ *(125)*. The existence of the methonium ion CH_5^+ is based not only on mass spectrometric studies[171] but also on the chemistry of methane in superacids and with strong electrophiles[172]. Thus, the interaction involves the main lobes of the covalent bonds (frontal attack). Since an electrophile will attack the points of highest electron density, attack will occur on the covalent bonds themselves and not on the relatively unimportant back lobes.

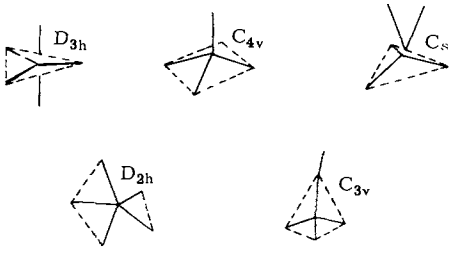


(125)

It should be remembered that the dotted lines symbolize the bonding orbitals of the three centered bonds and that

their point of junction does not represent an additional atom.

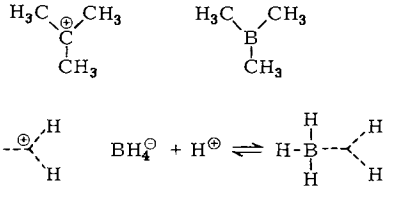
Of the possible structures for the methonium ion (D_{3h}, C_{4v}, C_s, D_{2h} or C_{3v} symmetry) *Olah*, *Klopman*, and *Schlosberg*[173] suggested preference for the C_s front-side protonated form. Preference for this form was based on consideration of the observed chemistry of methane in superacids (hydrogen-deuterium exchange and, more significantly, polycondensation indicating ease of cleavage to CH_3^+ and H_2) and also on the basis of self-consistent field (SCF) calculations[173]. More extensive calculations[174], including *ab initio* calculations utilizing an "all-geometry" parameter search[175], confirmed the favored structure with C_s symmetry. This structure is about 2 kcal/mol energy-poorer than the structure with C_{4v} (or D_{2h} or C_{3v}) symmetry, which in turn is about 8 kcal/mol energy-poorer than the structure with trigonal bipyramidal D_{3h} symmetry.



At the same time it should also be recognized that ready interconversion of stereoisomeric forms of CH_5^+ is possible by a pseudorotational-like process. *Muetterties* recently suggested naming stereoisomerization processes of this type in pentacoordinated compounds as "polytopal rearrangements"[176] (sometimes called "polyhedral rearrangements"). We, however, prefer to call intramolecular carbonium ion rearrangements as "bond to bond rearrangements" since these are not limited to equivalent bonds in the case of higher homologs of CH_5^+ (see subsequent discussion). Hydrogen-deuterium scrambling observed in superacid solutions of deuterated alkanes strongly indicate such processes.

4.3. Boron Analogs of Carbocations

It is of interest to note that isoelectronic boron compounds can be used as model compounds for both carbenium and carbonium ions. Trimethylboron has already been compared with the trimethylcarbenium ion (see Table 2) and it has recently been suggested that BH_5 may similarly be used as a model for comparison with CH_5^+[12].



BH_5 is formed in the acid hydrolysis of tetrahydroborates[177,178]. When the hydrolysis is carried out with deuterated acid, not only HD but also H_2 is formed. In strong acids the isotopic distribution is statistical. This is indicative of D^+ attacking the B—H bond (similarly to the attack of H^+ on methane) and of polytopal (bond to bond) rearrangement of BH_4D taking place, before subsequent cleavage occurs. The ease with which diborane exchanges hydrogen for deuterium when treated with deuterium gas[179] also indicates the formation of the three center bound analog, BH_3D_2.

$$B_2H_6 \rightleftharpoons 2\ BH_3$$

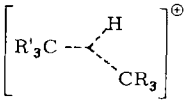
$$BH_3 + D_2 \rightleftharpoons H\text{-}B(H)(H)\text{---}D \rightleftharpoons H\text{-}B(H)(D)\text{---}H \rightleftharpoons BH_2D + HD$$

$$\Downarrow\Uparrow$$

$$B_2H_4D_2\ \textit{etc.}$$

4.4. Steric Effects in the Formation of Carbonium Ions

It should be emphasized that if steric interference (as is the case in interaction of tertiary C—H bonds in isoalkanes with tertiary carbonium ions) is substantial, the three-center bond of carbonium ions must be highly unsymmetrical, although the attack of the tertiary carbenium ion on the tertiary hydrogen of the isoalkane still cannot be considered to lie along an extension of the C—H bond (*i.e.* in a linear fashion)[180].



Similarly the protonation of sterically hindered C—C (and C—H) bonds can also only proceed *via* highly unsymmetrical carbonium ion states (see following discussion).

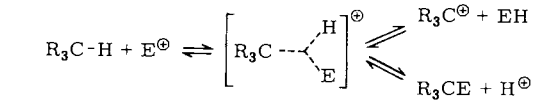
The preferred direction of attack by the electrophile should thus not be considered to be always the same and may very well vary from compound to compound (according to the reaction conditions). Since the possible configurations of pentacoordinated carbon do not differ very much in stability (as is also the case in CH_5^+), with exception of the "back-side" substituted trigonal bipyramid, which must be considered the least favorable form, it is unlikely that there is any "inherently" preferred pathway: it will depend on the individual reaction conditions; the electrophilic attack, however, always takes place on the appropriate bonds *via* "frontal" interaction.

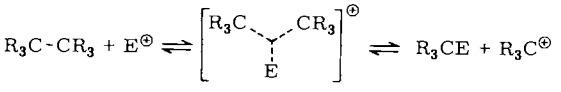
4.5. Electrophilic Reactions at Single Bonds: σ-Donor Systems

Pentacoordinated carbonium ions play an important role not only in connection with the structure of nonclassical ions, but more importantly in the general area of electrophilic reactions at single bonds, *e.g.* in the aliphatic substitution of alkanes and cycloalkanes. Such reactions include acid-catalyzed hydrocarbon isomerizations, fragmentations, cyclizations, and other transformation reac-

tions, electrophilic substitutions of alkanes and cycloalkanes and related electrophilic reactions.

We have in recent years obtained evidence for the general reactivity of covalent C—H and C—C single bonds of alkanes and cycloalkanes in various electrophilic substitution reactions such as protolytic processes, hydrogen-deuterium exchange[181], alkylation[180], nitration[182], halogenation[183] *etc.* This reactivity is due to what we consider, alongside n- and π-donor ability, the third major type of electron donor ability, *i.e.* the σ-donor ability (sigma basicity) of *bonded* electron pairs (*i.e.* single bonds) to share their electron pairs with an electron deficient reagent *via* two-electron, three-center bond formation. The reactivity of single bonds thus stems from their ability to participate in the formation of pentacoordinated carbonium ions. Subsequent cleavage of the three-center bond results in formation of trivalent carbenium ions and substitution products, or hydrogen (alkyl) transfer takes place.





$E^{\oplus} = D^{\oplus}, H^{\oplus}, R^{\oplus}, NO_2^{\oplus}, Hal^{\oplus}$

As to the nature of the transition state of the electrophilic reactions at single bonds, the experimental product compositions strongly favor pentacoordinated carbonium ion-type transition states involving carbocation centers with three regular covalent two-electron bonds and one two-electron three-center bond, which, in contrast with the linear or "back-side" attack, is formed *via* "frontal" attack[12, 180].

Frontal attack involving a trigonal transition state would lead to retention of optical activity if reactions were carried out at an optically active carbon center. Experiments presently being carried out in our laboratories appear, in part, to prove this, but there are many experimental difficulties in carrying out such reactions under controlled conditions. We have also been able to carry out electrophilic substitution reactions (deuteration, alkylation, nitration, chlorination) at bridgehead positions of rigid systems, such as adamantane, where back-side attack and olefin formation is impossible (for back-side attack the electrophile would need to pass through the cage structure). These reactions give direct experimental evidence for the frontal direction of the electrophilic attack and the nature of the pentacoordinated carbonium ion-type transition state[181, 182, 184].

4.6. Protolysis and Hydrogen-Deuterium Exchange

With superacids, alkanes readily undergo protolytic reactions involving tertiary, secondary, and primary C—H as well as C—C bonds[172, 181]. In the case of isoalkanes, tertiary C—H bond reactivity exceeds that of C—C bonds and secondary (and primary) C—H bonds. In *n*-alkanes, the C—C bond reactivity is generally found to exceed that of the C—H bonds. It is also apparent that steric factors affect σ-basicity as they do π- or n-basicity.

Bartlett, Condon, and *Schneider*[190] were the first to recognize that in aluminum halide catalyzed intermolecular hydrogen abstractions, the electrophile (carbenium ion or proton) can remove a tertiary hydrogen atom together with its bonding electron pair (the so-called hydride transfer reaction).

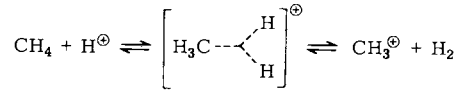
$$R_3C{-}H + R^{\oplus} \text{ (or } H^{\oplus}) \rightleftharpoons R_3C^{\oplus} + H{-}R \text{ (or } H_2)$$

In subsequent literature the assumption has generally been made that the hydrogen atom is removed with its electron pair through what amounts to a linear transition state.

Lewis, Hawthorne, and *Symons*[185] must be given credit for having first suggested that the transition state in hydrogen abstraction could be considered triangular instead of linear: "...electrophilic reagent attacks the C—H bond and the reasonable mode of attack is on the electrons of the bond. A triangular transition state is therefore proposed." This suggestion, however, went relatively unnoticed, mainly because there were no experimental data available to substantiate it and because it was considered that steric hindrance, particularly in the interaction of a tertiary carbenium ion with a tertiary isoalkane, would allow only linear interaction.

The question of the mechanism of the hydride abstraction was not further considered until 1967, when, with *Lukas* we reported on the protolytic ionization and hydrogen-deuterium exchange of alkanes and cycloalkanes in superacids such as FSO_3H—$SbF_5(SO_2ClF)$[45, 172a]. *Hogeveen,* in independent work, also made similar observations in HF—SbF_5 solutions[172c].

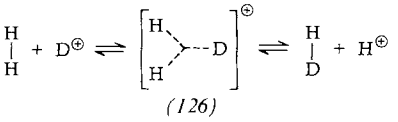
These studies demonstrated that in the new superacid systems not only tertiary and secondary, but also primary C—H bonds as well as C—C bonds undergo facile protolytic cleavage. To account for the observed protolytic reactions of alkanes, we suggested with *Klopman* and *Schlosberg*[173] that protolyses preferentially involve "front-side" attack through formation of triangular carbonium ions as shown in the case of protonation of methane to CH_5^+.



It appears, therefore, more reasonable to call these processes hydrogen abstractions (transfer) and not hydride abstractions, since *de facto* hydride ion is not involved in these processes.

Subsequently, we were able to show with *Shen* and *Schlosberg*[186] that molecular hydrogen (deuterium) itself readily undergoes hydrogen-deuterium exchange in superacids.

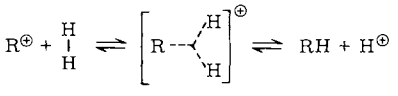
The reaction takes place even at room temperature, and we assume that a triangular H_3^+-transition state *(126)* is involved in the protolytic process.



(126)

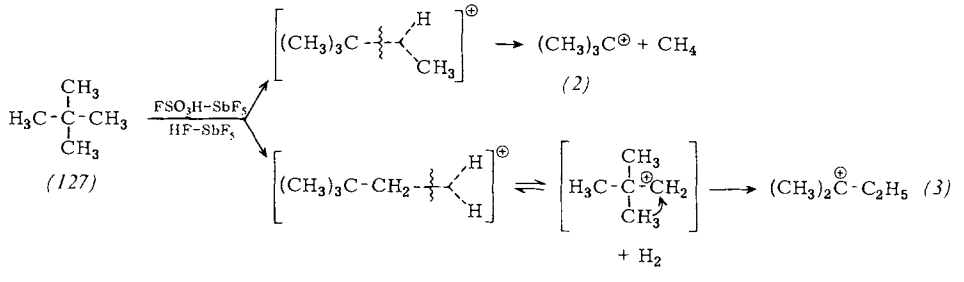
By way of contrast, *Hogeveen*[187a] initially rejected triangular transition states in hydride abstractions by arguing that such transition states would suffer considerable strain. Subsequently however, in collaboration with *Brouwer*, he favored bridged, unsymmetrical transition states[187b]. He also stated that he found no evidence for exchange of molecular hydrogen (deuterium) with the superacid system used (generally SbF_5 in a large excess of HF, which is a weaker acid system than the 1:1 acids used in our work), which he considered as further evidence against triangular transition states. At the same time he described the reaction of carbenium ions with molecular hydrogen[188]. He could not distinguish the nature of the transition state (linear *vs.* triangular) but considered the reaction to involve a linear transition state since no hydrogen-deuterium exchange was observed with molecular hydrogen (deuterium) itself.

$$R^{\oplus} + H{-}H \rightleftharpoons (R\cdots H\cdots H)^{\oplus} \rightleftharpoons R{-}H + H^{\oplus}$$



According to our studies of the hydrogen-deuterium exchange in superacids and the reaction of carbenium ions with hydrogen *i.e.* hydrogenolysis by carbenium ions, we suggested that they take place at the H—H bond, *i.e.* they represent alkylation of H—H by alkylcarbenium ions.

In our continued investigations it became obvious that protolysis of single bonds, including C—H as well as C—C bonds is a general reaction[181]. As example, the protolysis of neopentane *(127)* may be mentioned, where there is both C—C and C—H bond reactivity.



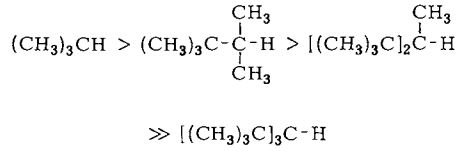
(127)

(2)

(3)

In FSO_3H—SbF_5 or SbF_5 (which generally always contains HF) C—H cleavage is favored at low temperatures (−80 °C). At higher temperatures or in HF—SbF_5, on the other hand, C—C cleavage predominates. This difference could be explained by the differing nature of the solvated proton ($H_2SO_3F^+$ or H_2F^+) which in superacids must be considered as a well defined, stable species.

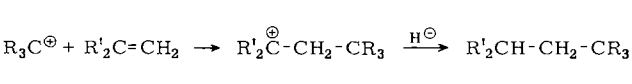
As is well known for of n- and π-basicities, steric hindrance can also influence the σ-basicity. If in isobutane the methyl groups are substituted by the much larger *tert*-butyl groups the reactivity of the tertiary C—H bond towards electrophilic reagents decreases rapidly. In the case of tri-*tert*-butylmethane this bond is already shielded to such a high degree that the tertiary C—H bond shows no reactivity at all, and electrophilic reactions, therefore, only occur on the C—C and the primary C—H bonds.



Due to the oxidizing ability of antimony pentafluoride (which is subsequently reduced to SbF_3), the possibility of one electron transfer redox processes must always be kept in mind when dealing with systems containing SbF_5. In superacids and particularly at low temperature the equilibrium concentration of SbF_5, for example in a HF—SbF_5 system, is low. Furthermore the protolytic reactivity of alkanes is well demonstrated using deuterated superacids. Electron transfer from an alkane single bond is a relatively high energy process necessitating 4—5 eV (*i.e.* > 100 kcal/mol) more activation energy then a comparable electron transfer process from a related alkene π bond and consequently is not very probable in low temperature solution chemistry. It is worth mentioning that many of the protolytic reactions discussed can also be carried out with acid systems other than those containing SbF_5. HF—TaF_5 and HF—BF_3 are, for example, useful superacids in such reactions. Since the redox potentials in these systems are high, it seems a well established fact that alkanes react in superacid solutions *via* single bond protolytic processes.

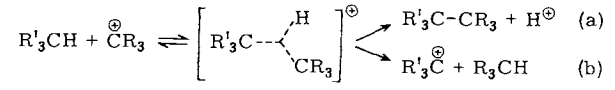
4.7. Alkylation

Despite frequent literature references to electrophilic alkylation of alkanes by olefins, from a mechanistic point of view these reactions must be considered as alkylations of the olefin by the carbenium ion formed from the isoalkane by intermolecular hydrogen transfer. Thus the alkane just serves as a reservoir for the alkylating agent.



The suggested reaction mechanism (*Schmerling*[189]) is reflected by the products formed in the reaction of propylene and isobutylene with isobutane. The products do not contain 2,2,3-trimethylbutane or 2,2,3,3-tetramethylbutane. These compounds would be expected as primary alkylation products in the direct alkylation of isobutane with propylene and isobutylene, respectively. As already discussed, in intermolecular hydrogen abstraction from a tertiary isoalkane by a carbenium ion, described by *Bartlett*, *Nenitzescu*, and *Schmerling*, the transition state could be considered either linear or triangular (from frontside attack on the C—H bond). The latter would under no circumstances be symmetrical because of steric interaction between the carbenium ion and the tertiary isoalkane. Even with a strongly distorted triangular transition state (*i.e.* assuming that the reaction takes place on the C—H bond itself and not at the back-lobe of the hydrogen atom), it becomes obvious that subsequent cleavage can result not only in intermolecular hydrogen transfer, but also, *via* proton elimination, in direct alkylation.

It should be emphasized that there is no necessity in suggesting a common transition state for hydrogen abstraction and alkylation, but only that triangular states of related nature are formed. As to which products are formed depends on the nature of the reactants, the reaction conditions, and the stability of the products, besides other factors such as strain in the formation of transition states, which affects the ratio of reactions (a) and (b).



R, R' = Alkyl

In the case of tertiary-tertiary systems (reaction of an isoalkane system with a *tert*-alkyl cation) a close to symmetrical trigonal three-center transition state would be too highly strained for its formation to be possible. However, it is unnecessary to consider a symmetrical transition state in the reactions. The tertiary carbenium ion could easily approach the tertiary C—H bond in such a way as to form an unsymmetric transition state, which can account for the great preference of intermolecular hydrogen transfer over alkylation in the reaction.

The possibility of preparing stable alkylcarbenium ions, permitted these reactions to be investigated under controlled "pure" conditions.

The reaction of stable, alkylcarbenium ions with alkanes can be advantageously studied in sulfuryl chloride fluoride solution at low temperatures (generally as low as $-78\,^{\circ}C$). A small amount ($\approx 2\%$ of C_8 fraction) of 2,2,3,3-tetramethylbutane was detected in the reaction of *tert*-butyl fluoroantimonate with isobutane[180].

$$(CH_3)_3C^{\oplus} + HC(CH_3)_3 \rightleftharpoons (CH_3)_3C{-}C(CH_3)_3 + H^{\oplus} \quad (128)$$

This observation is, however, of substantial importance since no other way than direct alkylation of the C—H bond of isobutane by the *tert*-butyl cation can account for formation of hexamethylethane *(128)*. That direct alkylation of alkanes indeed can be carried out with ease is further shown when isobutane is reacted with the less bulky isopropyl fluoroantimonate, or when propane is reacted with *tert*-butyl fluoroantimonate. The primary alkylation product 2,2,3-trimethylbutane is formed in up to 12% yield[180]. As intermolecular hydrogen transfer is faster than alkylation, and the isopropyl cation more reactive than the *tert*-butyl cation, the alkylation reaction in the system is considered to be mainly the propylation of isobutane.

$$(CH_3)_2CH_2 + \overset{\oplus}{C}(CH_3)_3 \rightleftharpoons (CH_3)_2CH^{\oplus} + HC(CH_3)_3$$
$$(CH_3)_3CH + H\overset{\oplus}{C}(CH_3)_2 \rightleftharpoons (CH_3)_3CCH(CH_3)_2 + H^{\oplus} \quad (129)$$

The alkylation products obtained are not only those derived from the starting alkanes and carbenium ion, but also those from the alkanes and carbenium ions formed by intermolecular hydrogen transfer. Generally this transfer reaction is a faster reaction than alkylation. Since carbocations also undergo isomerization, and since intermolecular hydrogen transfer produces new alkanes from these ions, it is obvious that increasingly more complex mixtures are going to be obtained. Generally the bulkier tertiary carbenium ions can attack the more shielded tertiary C—H bonds only with great difficulty. The processes mentioned, however, readily produce secondary and even incipient primary ions in the systems, which then substitute C—H bonds ("alkylation") or react with C—C bonds ("alkylolysis"). The alkylation reactions of alkanes produce a variety of products which, however, can be quantitatively analyzed by today's methods (gas chromatography, mass spectrometry). Since olefins are formed only to a minimal degree, if at all, under the reaction conditions when stable carbenium ion salts in low nucleophilicity solvents are used and since at low temperatures ($-78\,^{\circ}C$) and short reaction times (<30 sec), isomerizations are considered of lesser importance, we feel that indeed, for the first time, we have been able to study direct alkylation of alkanes. Product compositions, which indicate hydrogen transfer as well as primary and secondary alkylation but insignificant olefin formation or isomerization, support this claim. No similar product compositions have been observed in previous acid-catalyzed olefin alkylations. The alkylation of alkanes in competition with simultaneous hydrogen transfer can also be effected with the recently described $CH_3F{\rightarrow}SbF_5$[191] and $C_2H_5{\rightarrow}SbF_5$[192] complexes (which show incipient methyl and ethyl cation properties) and dialkylhalonium ions[193]. It is also reasonable now to suggest that in conventional Friedel-Crafts system direct alkylation can play a role, although in systems where olefin formation is possible, alkene reactivity vastly exceeds that of alkanes.

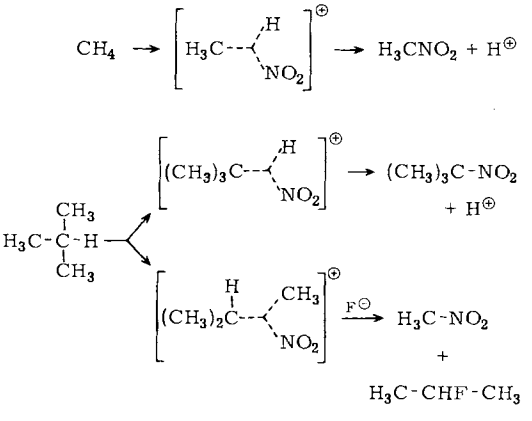
4.8. Nitration

The general concept of electrophilic reactivity of single bonds (σ donors) can be further demonstrated with a typical electrophilic reaction such as nitration. To avoid

the possibility of any free radical reaction resulting from the use of nitric acid and to avoid acid cleavage of reaction products, nitrations were carried out with stable nitronium salts, such as $NO_2^{\oplus}PF_6^{\ominus}$, in aprotic solvents such as methylene chloride-sulfolane[182]. In the case of methane and ethane (where the nitration product—nitromethane and nitroethane—is not acid-sensitive) anhydrous HF or FSO_3H were also used as solvents.

$$R{-}H \xrightarrow[CH_2Cl_2\text{-sulfolane}]{NO_2^{\oplus}PF_6^{\ominus}} R{-}NO_2 + H^{\oplus}$$

So far our studies have been directed primarily to mechanistic aspects. In methylene chloride-sulfolane solutions (which as n-bases compete with hydrocarbon σ-bases, such as methane) the yields are low (ranging from 1% nitration of methane at 25 °C through 2—5% nitration of higher alkanes, to 10% nitration of adamantane). In HF or HSO_3F solutions much higher yields of nitration of methane and ethane are obtained, but in the case of secondary and tertiary reaction products extensive protolytic cleavage reactions occur in acid media. In the electrophilic aliphatic nitronium ion nitration of alkanes the C—H and C—C bonds are once again the sites of attack; this results in substitution (*i. e.* nitration) or nitrolysis.



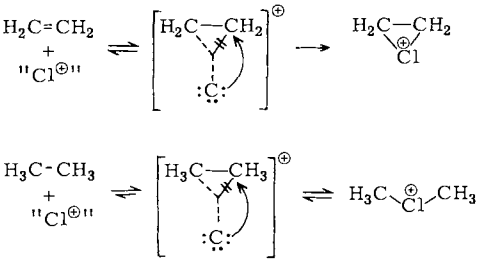
Since tertiary and secondary nitroalkanes are cleaved with ease by strong acids, aliphatic electrophilic nitration is affected by protolytic cleavage of products and therefore generally cannot be carried out in strong acid media without giving complex reaction mixtures.

4.9. Chlorination

Chlorination of alkanes can also be carried out under electrophilic conditions, *i. e.* Friedel-Crafts type acid-catalyzed chlorination, which takes place even at −78 °C in the dark[183].

In contrast to other electrophiles, the nature of positive halogens has not yet been sufficiently defined. We were able to carry out the chlorination of methane, ethane, propane, and higher alkanes in Cl_2—SbF_5—SO_2ClF solution at −78 °C in the dark. In this reaction, substitution products *(chlorination)* are formed as well as C—C cleavage products *(chlorolysis)*. The products formed can once again be explained as resulting from attack of the electrophile on the corresponding bonds with formation of a two-electron three-center bonded transition state. In the reaction of ethane with Cl_2—SbF_5 in SO_2ClF solution at low temperatures (*i. e.* under conditions favoring stable ions), for example, the main reaction products are the dimethylchloronium ion (chlorolysis) and the diethylchloronium ion (chlorination with subsequent formation of the chloronium ion).

Interestingly, in the case of electrophilic halogenations (such as chlorination) alkanes and alkenes act similarly as electron pair donors. The difference between the paraffins and the olefins in their reactions with "positive" chlorine, in which the unshared electron pairs of chlorine are also involved, is reflected in the type of reaction products formed. In the alkenes, where the σ-bonds are not involved in the reaction, three-membered cyclic halonium (chloronium) ions are formed whereas in the case of alkanes, where the C—C σ-bonds are involved directly in the reaction, open chain dialkyl chloronium ions are formed (chlorolysis).

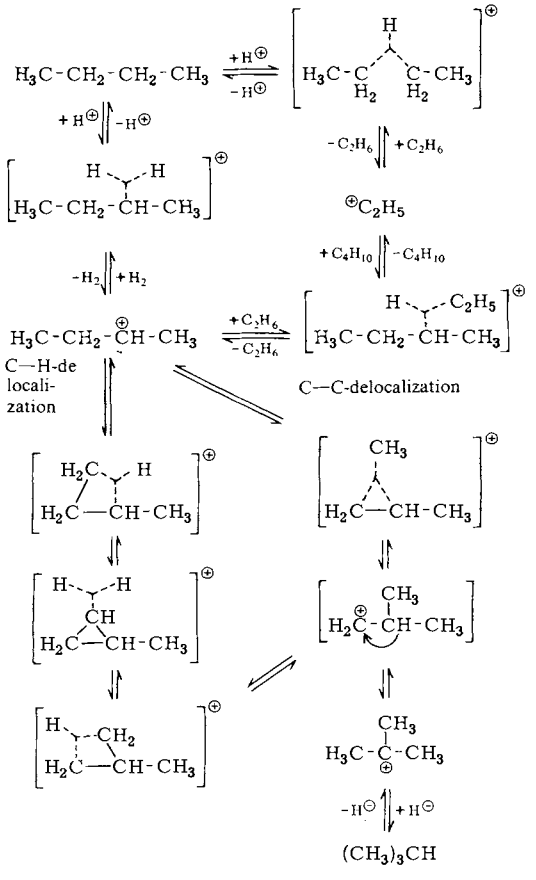


Alkanes also react in general (*i. e.* under conditions where the intermediate products are unstable) with chlorine in the presence of catalysts such as aluminum chloride, ferric chloride, and antimony pentachloride. Under the mild reaction conditions, these chlorides themselves show no chlorinating ability and are considered to act as true catalysts. (At higher temperatures and in the presence of light or free radical initiators ferric chloride, antimony pentachloride, and phosphorus pentachloride are chlorinating agents.) The reaction conditions used are not considered to favor radical formation, although it must be pointed out that electrophilic chlorine (Cl^+ or more probably Cl_2^+) can be considered as a radical cation (*i. e.* the triplet state). At the same time, the chlorine atom (Cl·) is a strong electrophile. Hence the differentiation between ionic and radical chlorine is not as clear as in the case of other substituting agents. Further, some catalysts such as PCl_5 coordinate weakly with molecular chlorine and could facilitate subsequent homolytic cleavage and thus radical chlorination.

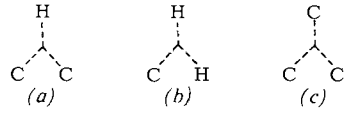
The Friedel-Crafts type chlorination of alkanes affords varying yields (2—5% in the case of methane but up to 55—60% in the chlorination of higher alkanes, including neopentane) and fairly high selectivity. In the chlorination of methane only methyl chloride is obtained (no methylene chloride or chloroform could be detected by gas chromatography). Stronger Lewis acid catalysts ($AlCl_3$, $FeCl_3$, *etc.*) cause increased dehydrochlorination of secondary and tertiary alkyl chlorides with subsequent chlorine addition leading to vicinal dichlorides.

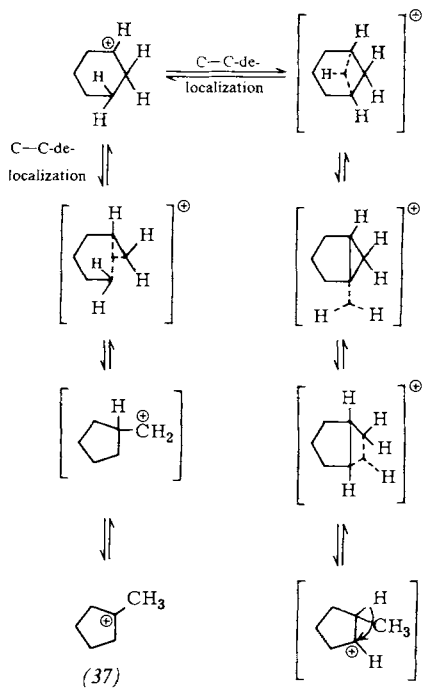
4.10. Rearrangements and Related Transformations

With a knowledge of the electron donor character of single bonds which leads to pentacoordinated carbonium ions it is now possible to explain the mechanisms of acid-catalyzed saturated hydrocarbon transformation reactions in those cases where no π- or n-donor reagents are involved which could themselves readily produce the needed initial carbenium ions. In such systems, for example in the isomerization of alkanes, the primary step is protolysis of a C—H or a C—C bond with formation of the corresponding carbonium ion transition state. (We have recently presented a detailed account of the mechanism of protolysis of alkanes[181].) In the following reaction step, with simultaneous cleavage of molecular hydrogen or of an alkane of lower molecular weight, an alkylcarbenium ion is formed which can subsequently undergo intra- or intermolecular processes (alkylation, alkyl or hydrogen shift, hydrogen transfer). These can all be considered to involve interaction of the electron-deficient carbenium center[194] with a C—C or C—H bond with formation of a new carbonium ion transition state. The typical carbocation processes can be shown, for example, in the isomerization of butanes[195].



A decisive role is played by protonated cyclopropanes in the rearrangement of the *sec*-butyl cation into the *tert*-butyl cation. The edge- and corner-protonated forms with three-center bonds of type *(a)* and *(b)*, respectively, can be differentiated from the methyl-bridged form [type *(c)*].



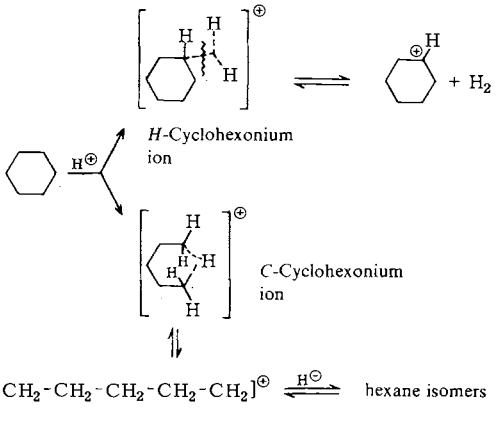


(37)

The skeletal rearrangements, however, must always take place with participation of the incipient primary isobutyl cation. Protonated cyclopropanes alone can not account for it, even though they are known to be involved in the hydrogen and carbon exchange (scrambling) processes.

Intramolecular alkylation processes (we have previously discussed well-defined intermolecular alkylations of alkanes by stable alkylcarbenium ions[180]) involving C—C or C—H bonds play a decisive role in ring contraction (or expansion) isomerizations, as, for example, in the isomerization cyclohexane ⇌ methylcyclopentane. Again, either C—H delocalized protonated cyclopropanes or C—C delocalized carbon bridged carbonium ion transition states can be involved.

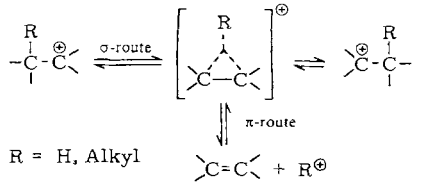
Whereas the cyclohexane-methylcyclopentane isomerization[196] involves initial formation of the cyclohexyl (methylcyclopentyl) cation (*i.e.* protolysis of a C—H bond) it should be mentioned that in the acid-catalyzed isomerization of cyclohexane up to 10% hexanes are also formed[196, 197]. This is indicative of C—C bond protolysis.



The observed protolytic behavior of cycloalkanes (and polycycloalkanes) in superacid solutions is indicative of either C—H or C—C bond protonation[198].

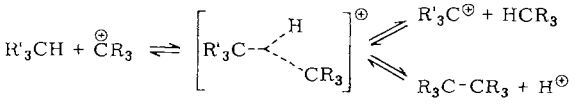
1,2-CH_3(alkyl) or hydrogen shifts (or the similar 1,3-, 1,4- or 1,5-shifts) in alkylcarbenium ions can also be considered as intramolecular alkylation of the C—C or C—H bonds by the carbenium ion center which leads to alkenonium ions. Hydrogen and alkyl bridged alkenonium ions are not observed in superacid solutions of rapidly equilibrating alkylcarbenium ions (*i.e.* by NMR, IR, Raman and ESCA spectroscopy[25, 30, 32, 36]); they are therefore probably only transition states or short-lived intermediates. However, it cannot be decided, as yet, whether alkenonium ion intermediates can exist.

Protolytic or alkylative three-center bond formation in carbonium ion processes can also explain cleavage and elimination reactions, particularly when the cleaving entity is a tertiary carbenium ion or proton; however, secondary and even primary ion cleavages are also observed. The close relationship between substitution, addition, and elimination reactions is thus obvious. Common (or closely related) carbonium ion transition states leading to carbenium ion intermediates are involved, which can be formed either by σ- or π-routes.



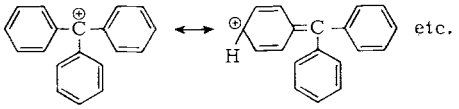
The β-cleavage reactions and deprotolytic olefin formations described by *Whitmore*[199] can also be considered as examples of three-center bound carbonium ion cleavages. *Schleyer*[200], as well as *Brouwer* and *Hogeveen*[201], have called attention to the importance of orientation of adjacent C—H or C—C bonds relative to the vacant p-orbital of carbenium ion centers in intramolecular carbocation reactions (such as 1,2-shifts and β-cleavages). In our opinion the orientation of the vacant p-orbital should be considered with regard to formation of a two-electron three-center bonded carbonium ion transition state.

As already discussed we were recently able to show that the fundamental intermolecular hydride transfer process described by *Bartlett*, *Nenitzescu*, and *Schmerling*[189, 190] involves a three-center bound carbonium ion transition state[181] and not, as has been generally assumed, a linear transition state[202]. Even in the sterically highly unfavorable reaction of isobutane with the *tert*-butyl cation, in addition to fast intermolecular hydrogen transfer, formation of small amounts of the alkylation product 2,2,3,3-tetramethylbutane *(129)* was also observed[180]. This



(129), R = CH_3

strongly indicates the triangular nature of the transition state. In the frequently used hydrogen abstractions with triphenylmethyl cations[203] (such as in the preparation of tropylium salts from cycloheptatriene[204]) the hydride abstracting agent may not always be the tertiary carbenium ion site. When perdeuteriotriphenylmethyl cation was allowed to react with cycloheptatriene to form tropylium ion, the triphenylmethane formed in the reaction showed protium substitution in the *para* (and *ortho*) ring positions. Hence, not only the tertiary carbenium ion center, but also secondary benzenium ion centers contributing to the stabilization of triarylmethyl cations, participate in the reaction[205].



(40a) *(40b)*

A somewhat similar situation has emerged from recent reinvestigation of *Gomberg*'s triarylmethyl radicals[206].

4.11. The Question of Hyperconjugation

Finally one can raise the question just how much a partially developed intramolecular three-center carbonium ion bond participates in hyperconjugation and the stabilization of carbenium ions. C—H and C—C hyperconjugation are simply explained by this term (where C—C hyperconjugation should play a more important role than C—H hyperconjugation). It should be clear, however, that in three-center bond formation the relative positions of the nuclei involved in this bond (compared to the starting compounds) must change *i.e.* there are indeed new bonding states developed which subsequently can lead to bridging.

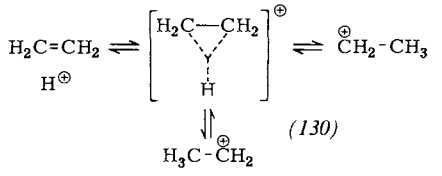
In contrast the stabilization of carbenium centers can also take place by σ-π electronic interaction without changes in bond lengths and angles, *i.e.* without extensive motion of the nuclei. This situation was described by *Traylor*[209a] as vertical stabilization (in the Frank-Condon sense). There is, however, no reason to believe that a dichotomy should exist between participation with and without bridging. The hyperconjugative interaction will always be accompanied by some geometrical change, but the extent of that deformation may be small or large (depending on the specific system).

4.12. Concerning the Mechanism of Electrophilic Reactions of π-Donor Systems

The reactivity of olefins, acetylenes, and aromatic hydrocarbons toward electrophiles in addition and substitution reactions is based on the π-electron donor ability of the unsaturated C=C or C≡C bonds and the π-aromatic systems[170a, 207].

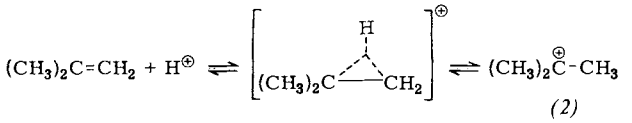
In the reactions discussed so far we have emphasized the importance of formation of two-electron, three-center bonds in pentacoordinated carbonium ion formation utilizing the electron pair of single σ-bonds. Two-electron, three-center bond formation is also considered to be involved in the initial step of electrophilic reactions of π-bonded systems.

Protonation of olefins, the essential first step in acid-catalyzed isomerizations, alkylation, hydration, and related addition and substitution reactions, is considered to involve the initial overlap of the two carbon atom p-orbitals (of the π-bond) with the empty s-orbital of the proton forming the two-electron, three-center bond of the ethyleneprotonium ion *(130)*, a hydrogen bridged carbonium ion[208].



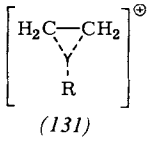
(130)

In protonated higher olefins the three-center bond formation should, because of electronic and steric effects, be unsymmetrical (oriented). Furthermore, both theoretical calculations[209] and lack of experimental observation indicate that bridged alkeneprotonium ions (as well as "alkenealkonium" ions) can exist only as high energy transition states, not as intermediates, but no decision can be made on this point as yet[209]. Subsequent opening of the three-center bond gives the carbenium ion intermediates of highest stability (which explains the empirical Markownikoff rule).

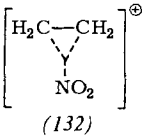


(2)

Alkylation, nitration, *etc.* of π-bonds is also considered to involve similar interactions with formation of tetracoordinated carbonium ion transition states *(131)* and *(133)* with three-center bonds.

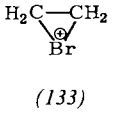


(131)

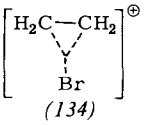


(132)

In contrast the long-lived ethylenebromonium ion *(133)* and other alkenehalonium ions are not three-center bound ions, but three-membered cyclic halonium ions with covalent C-halogen bonds[210]. These ions are clearly intermediates and the three-center bound halonium ions such as *(134)*—similar to previously discussed ions—could

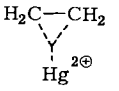


(133)



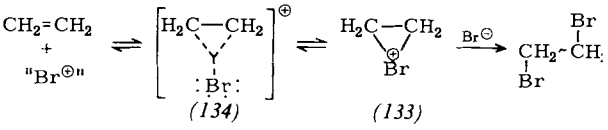
(134)

be the transition states leading to them; however, the existence of three-center bonded halonium ion intermediates cannot be ruled out. Distinction between the two different types of alkenonium ions is not always clear, although it could be, for example, in the case of observable intermediates by comparison of the NMR spectra. NMR data of the observed three-membered ring halonium ions and the three-center bound ethylenemercurinium ion *(135)*[211] (which can serve as model compounds) are quite different. [*(134)*, $\delta_H = 5.53$, $\delta_{^{13}C} = 120.8$; *(135)*, $\delta_H = 7.68$, $\delta_{^{13}C} = 57$.] Even if in the latter case the bonding is somewhat different (due to additional d-orbital participation) to what would be the case in a three-center bound halonium ion, increased p-character of the carbon atomic orbitals in a tetracoordinated carbonium ion should be reflected by substantial deshielding of the chemical shifts (caused also by higher charge density on these atoms).



(135)

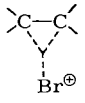
In electrophilic halogen additions to olefins the electrophilic halogen is considered to interact through its vacant atomic orbital with the π-electron pair of the olefin to form a two-electron three-center bonded ion (or probably transition state). Opening of the three-center bond and simultaneous participation of the halogen non-bonded electron pairs then gives the three-membered halonium ion intermediate (which can be spectroscopically observed and also isolated). Subsequent displacement by halide ion from the back-side results in the generally observed *trans* stereospecificity of the addition.



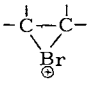
(134) *(133)*

An alternate route can be considered for the initial interaction between olefin and bromine: polarized molecular bromine reacts with the π-bond through overlap of the back-lobe of the antibonding molecular orbital of the bromine to give the three-center bound transition state.

Strating, Wieringa, and *Wynberg*[212] recently isolated a bromonium ion salt of adamantylideneadamantane. Recent studies by with *Schilling, Westerman,* and *Lin*[212a] by ^1H and ^{13}C-NMR spectroscopy have shown that the Br_2 and Cl_2 complexes of adamantylideneadamantane, as the Ag^+ complex, are indeed three-center bound



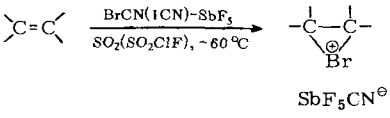
π-complex



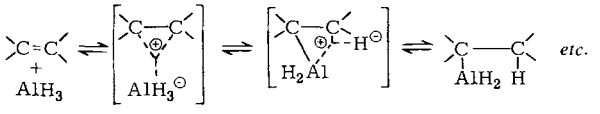
σ-complex

alkenonium ions (π-complexes), whereas the H^+ complex (in superacids) is the rapidly exchanging (equilibrating) alkenium ion (σ-complex). Thus, for the first time a direct differentiation of alkenium (σ-complex) from alkenonium ions (π-complexes) was achieved in electrophilic reactions of alkenes (even if highly hindered ones).

We have also been able to achieve the first direct preparation of cyclic three-membered σ-bound halonium ions by electrophilic halogenation of less hindered olefins by reacting tetramethylethylene and ethylene, respectively, with cyanogen iodide (bromide) in presence of SbF_5 in SO_2 or SO_2ClF solution at −78 °C.



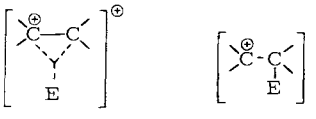
In electrophilic reactions of various π-bonded systems the electrophiles can be defined in a broad sense according to the generalized Lowry-Brønsted concept. Addition reactions, for example, are equally well carried out with various cationic reagents or Lewis acids, such as BH_3[213] or AlH_3[214] (*Brown* hydroboration[213] or *Ziegler* hydroalanation[214]).



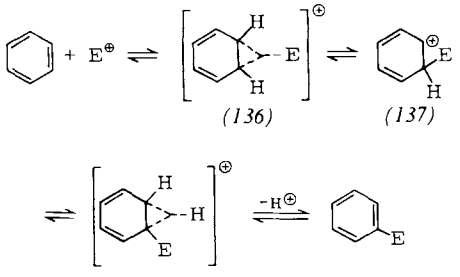
Since the B—H or Al—H bonds act as internal nucleophile during opening of the three-center bond it is clear why hydroboration and hydroalumination show *cis* stereospecificity whereas halogen additions generally proceed by *trans* addition.

Electrophilic reactions by Lewis acid type reagents on σ-bonds are considered less favorable, since the weaker electron donor σ-electron pair is generally not able to form carbonium ions *via* electron pair sharing with Lewis acids (which frequently are dimeric or polymeric halogen bridged reagents like aluminum or antimony halides, and become electron deficient reagents only on breaking the halogen bridges). That is the reason why Friedel-Crafts catalyzed hydrocarbon reactions generally need co-catalysts to provide protic or carbocationic reactivity.

Electrophilic additions to olefins can be considered, in accordance with the Hammond postulate[215], to involve transition states resembling either the intermediate trivalent carbenium (or, in the case of halogenation, three-membered ring halonium) ions or starting olefins. In the first case the new covalent bond is more developed in the transition state than in the latter. Thus the position of the transition state is not fixed and can vary along the reaction path and can resemble either starting olefin or carbenium ion intermediate.



A similar situation is found in aromatic electrophilic substitutions[216]. Once again, in these reactions we must assume the electron donor ability of a π-electron pair towards the electrophile will result in formation of a tetracoordinated three-center bonded benzonium ion *(136)* (π-complex type transition state). Subsequent cleavage of the three-center bond gives a trivalent benzenium ion *(137)* (σ-complex intermediate). The transition state, once again, can either resemble starting aromatics (when it lies early on the reaction coordinate) or be of arenium ion nature (in case of late transition states). For a more detailed discussion of the mechanism of electrophilic aromatic substitution see a recent review [216].



π-Electron pairs are, of course, stronger electron donors than σ-electron pairs. In systems containing both π- and σ-bonds, therefore, the π-system is generally the reactive site. For example, in toluene, electrophilic reactions lead to substitution at the ring and not at the methyl group. However, if we make the π-system less available (either by deactivating groups or by steric crowding) the σ-bonds of the methyl group can become more reactive. Thus pentafluorotoluene undergoes electrophilic reactions on the methyl group[217].

Similar considerations are also valid for the reactivity of deactivated or sterically hindered olefins and other π-donor systems.

Dewar[218] should be credited with having advanced the concept of "π-complex" interaction of electrophiles with π-donor systems as far back as in the 1940's. π-Complexes were, however, generally regarded only as weak donor/acceptor interactions between the π-donor system and the electron-deficient reactant. *Dewar*, however, considered them as much stronger "molecular bonds", the π-electron pair overlapping with the electron-deficient species' empty orbital. In 1965, when discussing "nonclassical ions" as π-complexes, *Dewar* and *Marchand*[219] stated, "...in a true π-complex, the π-donor and acceptor are linked by a covalent bond, not by weak forces of van der Waal's type." Dewar's π-complexes indeed are carbonium ions (alkonium ions) involving two-electron, three-center bonds, with the π-system supplying the electron pair for the bond.

It should be emphasized that the chemical literature contains in many instances suggestions for bridged (symmetrical or unsymmetrical) cationic intermediates, besides Dewar's π-complexes. For example, *Taft*[208] suggested that the protonation of olefins leads first to a separate π-bonded species which subsequently can transform into a carbenium ion. *Ingold*[220], *Winstein*[221], *Bartlett*[222], *Cram*[223], *Stiles*[224], *Berson*[225], *Allen*, *Schleyer*, and *Pople*[226] as well as other investigators have on different occasions discussed in considerable depth the question of bridging in carbocations. Only our recent studies, however, have

shown that the unifying principle of all electrophilic reactions is indeed the general donor ability of the bonded electron-pairs of either π- or σ-bonds to form, with the vacant orbital of the electrophile, triangular two-electron three center bound carbonium ions (transition states or intermediates), which subsequently can give trivalent carbenium ions or lead to substitution (addition) products[12].

5. Outlook

In conclusion, the differentiation of trivalent carbenium from penta- or tetracoordinated carbonium ions, based on their direct observation, showing marked differences, for example, in their NMR and ESCA spectra, should put an end to much of the "myth" surrounding organic cations and to the so-called "classical-nonclassical ion controversy". In defining limiting categories of carbocations it must be clearly understood, of course, that there exists the possibility of a whole spectrum of ions or intermediate degrees of delocalization (or partial "nonclassical" nature) and therefore division in strictly limiting categories frequently is arbitrary. Whereas the norbornyl cation itself, for example, is a completely symmetrically delocalized nonclassical carbonium ion, the 2-methylnorbornyl cation shows partial delocalization. More importantly, the concept of pentacoordinated carbonium ion formation *via* electron sharing of single bonds with electrophilic reagents in three-center bond formation promises to open up a whole new important area of chemistry. Whereas the concept of tetravalency of carbon obviously is not affected, carbon penta- (or tetra-)coordination as a general phenomenon must be recognized. Trivalent carbenium ions play a major role in electrophilic reactions of π- and n-donors, whereas pentacoordinated carbonium ions play an equally important similar role in electrophilic reactions of σ-donor saturated systems. Accordingly electron donors can be categorized into the following types:

Types of electron donors

π-Donors bonded (shared) electron pair donors	σ-Donors	n-Donors non-bonded (unshared) electron pair donors
alkenes alkynes aromatics	alkanes single bonds of all types, such as C—H, C—C, H—H, *etc.*	hetero-atoms, such as O, S, N, Hal *etc.* carbanions

The realization of the electron donor ability of shared (bonded) electron pairs (single bonds) could one day rank equal in importance with *G. N. Lewis*' realization[227] of the importance of the electron donor unshared (non-bonded) electron pairs. We can now not only explain the reactivity of saturated hydrocarbons and single bonds in general in electrophilic reactions, but indeed use this understanding to explore many new areas and reactions of carbocation chemistry.

Finally, I would like to point out that my review deals primarily with the structural problems of carbocations based on the direct (spectroscopic) observation of long-lived ions and the role carbocations play in the course of electrophilic reactions. No attempt has been made to give a complete survey of this very large and active field. I would, therefore, like to apologize to all those colleagues working in this field whose important contributions have not been mentioned. The choice of material was strongly influenced by limitations of space and my own interests and should not be assumed as a critical evaluation. Our own studies were inevitably strongly emphasized and served as a basis for development of the general concepts presented.

Support of our work by the National Science Foundation, the Petroleum Research Fund administered by the American Chemical Society, the U.S. Army Research Office, and the National Institutes of Health, US Public Health Service is gratefully acknowledged. My particular thanks go to all members of my research group (past and present) whose enthusiastic hard work really made our studies possible. Their names are found in the references.

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[3] For reviews see *G. A. Olah*, Chem. Eng. News *45*, p. 76 (March 27, 1967); Science *168*, 1298 (1970).

[4] Existence is defined by Webster (Third New International Dictionary, Unabridged Edit., Merriam Co., 1961, p. 796) as: "The state or fact of having being, especially as considered independently of human consciousness."

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[29] Magic acid® [27b] is a registered trade mark of Cationics, Inc. 653 Alpha Drive, Cleveland, Ohio 44143 (USA) and is available, together with other superacids and cationic reagents, from this company as well as from Aldrich Chemical Co.

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[197] *D. P. Stevenson* and *J. H. Morgan,* J. Amer. Chem. Soc. *70,* 2890 (1948).

[198] *G. A. Olah* and *J. Lukas,* J. Amer. Chem. Soc. *90,* 933 (1968).

[199] *F. C. Whitmore,* J. Amer. Chem. Soc. *54,* 3274 (1932); *F. C. Whitmore* and *E. E. Stahly, ibid. 55,* 4153 (1933); *F. C. Whitmore,* Chem. Eng. News *26,* p. 668 (March 8, 1948).

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[203] *H. J. Dauben, Jr., F. A. Gadecki, K. M. Harmon,* and *D. L. Pearsen,* J. Amer. Chem. Soc. *79,* 4557 (1957).

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[205] Experimental results supporting this suggestion were recently reported by *G. A. Olah* and *J. J. Svoboda,* Manchester Meeting of the Chemical Society, April 1972; J. Amer. Chem. Soc., in press.

[206] *H. Lankamp, W. T. Nauta,* and *C. MacLean,* Tetrahedron Lett. *1968,* 249.

[207] For general discussion see, for example, *J. March:* Advanced Organic Chemistry Reactions, Mechanisms and Structure. McGraw-Hill, New York 1968.

[208] *R. W. Taft, Jr.* (J. Amer. Chem. Soc. *74,* 5372 (1952)) seems to be the first to have suggested the initial formation, in the acid catalyzed hydration of isobutylene, of a proton π-complex of the type described originally by *M. J. S. Dewar* (J. Chem. Soc. *1946,* 406 and Bull. Soc. Chim. France *1951,* C 75) in which "...the proton is embedded in the π-orbitals which extend above (or below) the plane of the C—C double bond".

[209] For theoretical aspects see *L. Radom, J. A. Pople, V. Buss,* and *P. v. R. Schleyer,* J. Amer. Chem. Soc., in press.

[209a] *T. G. Traylor, W. Hanstein, H. J. Berwin, N. A. Clinton,* and *R. S. Brown,* J. Amer. Chem. Soc. *93,* 5715 (1971); *W. Hanstein, H. J. Berwin,* and *T. G. Traylor, ibid. 92,* 829 (1970).

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[212a] *G. A. Olah et al.*, to be published.

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[222] *P. D. Bartlett:* Nonclassical Ions. Reprints and Commentary. Benjamin, New York 1965, and the numerous references cited therein.

[223] *D. J. Cram*, J. Amer. Chem. Soc. *71*, 3863 (1949) and subsequent publications; see also *D. J. Cram*, *ibid. 86*, 3767 (1964).

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[225] *J. Berson* and *S. Suzuki*, J. Amer. Chem. Soc. *81*, 4088 (1959).

[226] *J. E. Williams, Jr., V. Buss, L. C. Allen, P. v. R. Schleyer, W. A. Lathan, W. J. Hehre*, and *J. A. Pople*, J. Amer. Chem. Soc. *92*, 2141 (1970); *G. V. Pfeiffer* and *J. C. Jewett*, *ibid. 92*, 2143 (1970).

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Polar Cycloadditions[**]

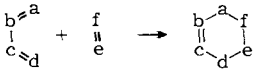
By Richard R. Schmidt[*]

Cycloadditions with ionic components are known as "polar cycloadditions" to distinguish them from cycloadditions with dipolar and uncharged components. The structural requirements, the manner in which "polar" intermediates capable of addition are produced and their reactivity with activated and nonactivated multiple bonds, the many peculiarities of the course of the cycloaddition, and the favorable synthesis of heterocyclic systems by this reaction principle makes such a terminological distinction useful and necessary if the existing data are to be brought into order. The present review, which is the first on a field of chemistry that has not yet been very extensively investigated, deals initially with cationic and then with anionic polar cycloadditions.

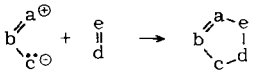
1. Introduction

1.1. Polar Cycloadditions—Definition

Cycloadditions with uncharged [eq. (1)] and dipolar components [eq. (2)] are widely known synthetic principles. Between these there are cycloadditions with positively and negatively charged ionic components, whose reactivity is



(1)



(2)

due primarily to their electrophilic or nucleophilic character. These reactions will be classified as "polar cycloadditions" [eq. (3a) and (3b)][*][1]. They are of interest in particular for the feasible synthesis of heterocycles, the inclusion of nonactivated multiple bonds in the scope of the reaction, and the numerous questions raised by following this synthetic route.

It is suggested that the number of ring atoms contributed by the ionic or "polar" components[**] and also the charge on the reactive centers should be indicated by descriptions such as $[4^{\oplus}+2]$ and $[3^{\ominus}+2]$ cycloadditions[***].

However, this tells us nothing about the reaction mechanism. The intermediate position of polar cycloadditions between those with uncharged components and those with dipolar ones is not merely formal. Thus transitions from synchronous (*i.e.* simultaneous, though not necessarily equally fast) to non-synchronous formation of the new σ bonds to give the cycloadduct are often observed here;

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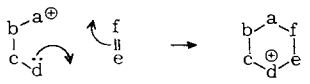
[**] Note added in proof: The importance of this reaction principle has recently been further demonstrated by *Eschenmoser* [148], *Ghosez* [149], *Huisgen* [150], *Schöllkopf* [151], *Corey et al.* [152], and some other research groups.

[*] A few examples were compiled earlier and their peculiarity stressed; see Ref. [7], pages 607, 608.

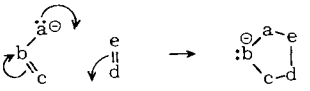
[**] The number of ring atoms contributed by the individual components has been used by *Huisgen* [2] for the classification of cycloadditions.

[***] Cycloadditions with uncharged components, such as Diels-Alder reactions, can then be described, as in the past [2], as [4+2] cycloadditions, and *e.g.* dipolar 1,4-cycloadditions are distinguished from these by designation as $[4^{\oplus}+2]$ cycloadditions; see also [3].



(3a)

$[4^{\oplus} + 2]$-Cycloaddition



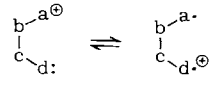
(3b)

$[3^{\ominus} + 2]$-Cycloaddition

the "conservation of orbital symmetry"[4] as an energy factor for the occurrence of the reaction is then outweighed by other energy factors, and the new σ bonds, as in many electrophilic and nucleophilic additions, are formed consecutively. For mechanistic differentiation, therefore, in synchronous reactions controlled by orbital symmetry after *Woodward* and *Hoffmann*[4], the type of orbital, the number of electrons present, and the steric participation in the reaction are indicated, insofar as they have been investigated and discussed; the course of the reaction, *i.e.* electrophilic or nucleophilic addition, is also denoted.

The polar systems capable of cycloaddition frequently cannot be isolated, but must be produced *in situ* from neutral molecules. If the formation of the new σ bond begins when the bond to the leaving group is still only partly broken, cationoid or anionoid instead of free polar systems occur as intermediates of the cycloadditions. Contact ion pairs and solvent-separated ion pairs are therefore possible intermediates of these reactions and the influence of the solvent on the course of the reaction should be large.

The polar systems may also form diradical-cations; an example is shown in eq. (4). This possibility, which has so far been considered mainly theoretically (see Section 2.5 and Ref.[133]), will not be discussed here.



(4)

In this review, the reaction principle of "polar cycloaddition" will be derived for the case of $[4^{\oplus} + 2]$ cycloadditions and then extended to other types of reactions. Mechanistic criteria cannot be used for the subdivision of the subject matter, owing to the many possibilities available. The structural variation of polar systems having the same charge and the same number of centers yield important knowledge for the understanding of these reactions; this is therefore taken as the essential basis for the subdivision of the material. The variation of the number of centers of polar systems having comparable structures and equal charges also has interesting aspects; this is illustrated by an example in Section 2.5.

1.2. Cycloadditions with Uncharged and Dipolar Components

Before discussing polar cycloadditions, let us briefly consider thermal cycloadditions with uncharged and dipolar components.

The synthesis of three-membered and four-membered rings is limited to the cycloaddition of sextet centers[5] (carbenes and nitrenes) and the cycloaddition of particularly reactive enes and heteroenes[4,6] (ketenes, isocyanates, *etc.*) to multiple bonds. Many five-membered heterocycles are obtainable by 1,3-dipolar cycloadditions[7]. The dimerization of 1,3 dipoles is only of limited use for the synthesis of six-membered heterocycles. The Diels-Alder synthesis has not attained the same importance for heterocycles[8] as for carbocycles. An important synthetic principle for heterocycles is the 1,4-dipolar cycloaddition[9,10]. Larger rings can be prepared by cycloadditions with uncharged components or dipoles only in isolated cases[4].

The main factors that determine this situation are as follows:

a) Uncharged systems with more than two conjugated multiple bonds (*e.g.* conjugated trienes) and particularly dipolar species with more than four centers (*e.g.* 1,5 dipoles) frequently change into the ring form in an irreversible electrocyclic reaction. Moreover, cycloaddition reactions are hindered by the molecular geometry of such systems.

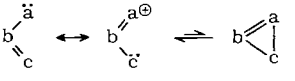
b) In cycloadditions, new σ bonds are generally formed at the cost of energy-rich π bonds. Most hetero-multiple bonds are in comparison poorer in energy than the corresponding CC multiple bonds (see Table 1); they are therefore less suitable for cycloadditions to nonpolar components.

Table 1. Average bond energies in kcal/mol[a].

C—C	83	C—N	69.7	C—O	84.0
C=C	147	C=N	147	C=O	164
C≡C	194	C≡N	207		

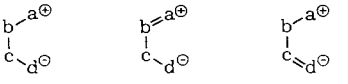
[a] *L. Pauling:* The Nature of the Chemical Bond. Cornell University Press, Ithaca, N.Y.

c) Of the dipolar intermediates, only the 1,3 dipoles are ideal cycloaddition reactants, since the valence-tautomeric three-membered ring, because of its high ring strain, is often richer in energy than the 1,3 dipole, which is comparable to the conjugated dienes [eq. (5)][7,11].

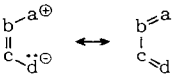


(5)

On the other hand, the production of 1,4-dipolar species is subject to very strict structural conditions. The two charges must be separated by quaternary centers, so that the energy-rich 1,4 dipole [of the type (6)] cannot change into the diene [of the type (7)], which is poorer in energy. The localization of the charges generally leaves little room for cycloaddition reactions between the irreversible intramolecular cyclization and the excessive stabilization of the



(6)



(7)

charges by appropriate substituents. The isolation of 1,4 dipoles that are capable of addition is therefore particularly important[10][*].

d) With the exception of carbenes and nitrenes the above mentioned cycloaddition components generally react only with activated multiple bonds[7].

However, as is well known, electron withdrawing and electron releasing substituents promote cycloadditions and Lewis acids are good catalysts for some of these reactions. Therefore, the more electrophilic or nucleophilic positively or negatively charged cycloaddition components should react with nonactivated multiple bonds. The polar cycloadditions demonstrate this valuable extension of the reaction scope to less reactive π-systems in many instances.

2. Cationic Polar Cycloadditions

2.1. [$4^{\oplus}+2$] Cycloadditions

2.1.1. The Structure of Polar 1,4 Systems

A cationic polar 1,4 system is defined as a compound a—b—c—d that has a sextet of electrons and a positive formal charge on a. There is at least one lone pair of electrons on d, or there is a pair of π electrons between c and d. The polar 1,4 system can form a cycloadduct with a multiple bond system e=f or e≡f. Center d or c then carries a positive formal charge in the cycloadduct.

The delocalization of the charge over several atoms is an important energy factor in the occurrence of these reactions. However, the cycloadduct is frequently stabilized by rearrangement or removal of a positive residue. The definition of the term "cycloaddition" by *Huisgen*[2], which excludes the elimination of small molecules or ions in the cycloaddition step, marks some of the polar cycloadditions discussed below as limiting cases.

The above definition allows at least the seven structurally different polar 1,4 systems *(1)* to *(7a)*. The two reactive centers a and d in these systems will generally react independently of each other (unless the relatively small interaction of orbitals *via* σ bonds[12] provides a reaction-determining energy contribution, for which there is as yet no experimental evidence in polar systems[13]):

a) The orbitals on a and d available for the formation of the new σ bonds are separated by tetragonal centers in *(2)*, *(3)*, *(5)*, and *(7)*.

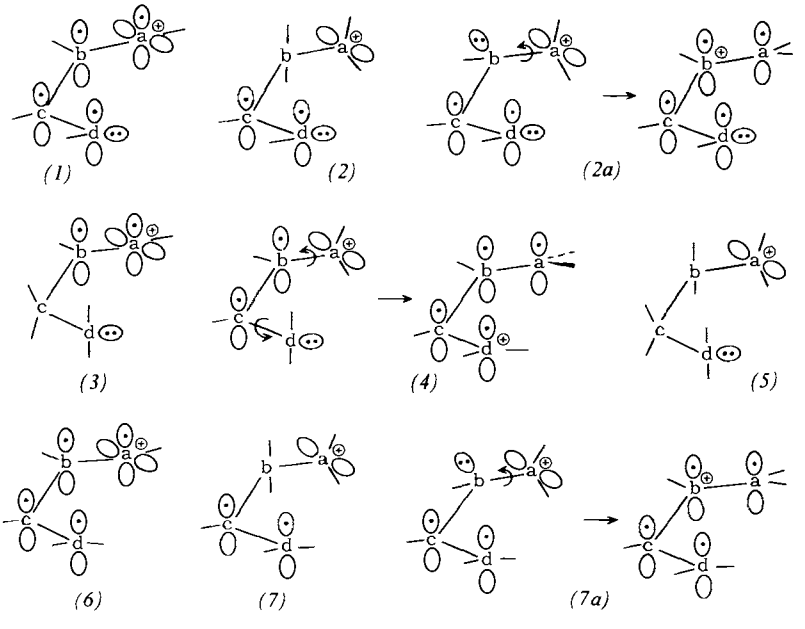
b) Though there is a conjugated 4π system in *(1)* and *(6)*, the empty vinyl cation orbital on a, which is orthogonal to the 4π system and to the non-bonding electron pair on d, is more reactive.

The situation is changed in the system *(4)* and in the systems *(2)* and *(7)* if b represents an atom with a non-bonding pair of electrons [≙ *(2a)* or *(7a)*]:

The orbitals available on a and d for the formation of the new σ bonds are coupled by π-electron resonance, and the system as a whole is stabilized by charge delocalization, so that Diels-Alder-like components are present. Synchronous cycloadditions, which follow the Woodward-Hoffmann rules[4], may now be energetically favored.

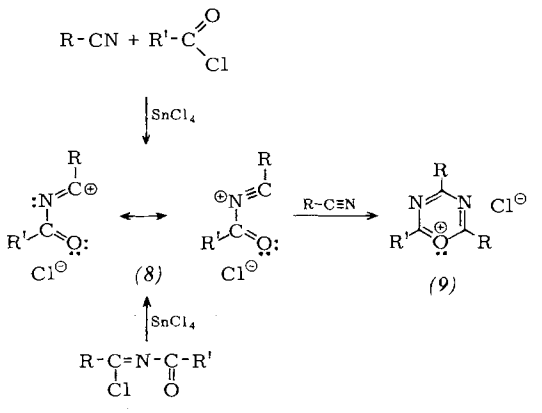
2.1.2. [$4^{\oplus}+2$] Cycloadditions *via (1)*

The reaction of acyl chlorides with nitriles in the presence of Lewis acids leads to 1,3,5-oxadiazinium salts *(9)*[14,15]. Since *N*-acylimidoyl chlorides also give *(9)* with nitriles and tin(IV) chloride[15], these reactions may, according to *Meerwein et al.*[16], be assumed to involve *N*-acylnitrilium ions *(8)* as intermediates. The cations *(8)* generally cannot

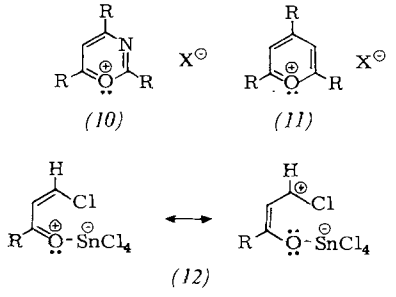


be isolated; they add to further nitrile to form the heteroaromatic compound *(9)*[15].

[*] 1,1 and 1,2 dipoles that are capable of cycloaddition cannot be produced, unless *e.g.* singlet-sextet centers are designated as 1,4 dipoles.



This reaction has been extended to cyanates[17] and cyanamides[18]. Acetylenes can also be used as cycloaddition partners; the 1,3-oxazinium salts *(10)* obtained in this way[15,19,20] are interesting intermediates for syntheses[21].



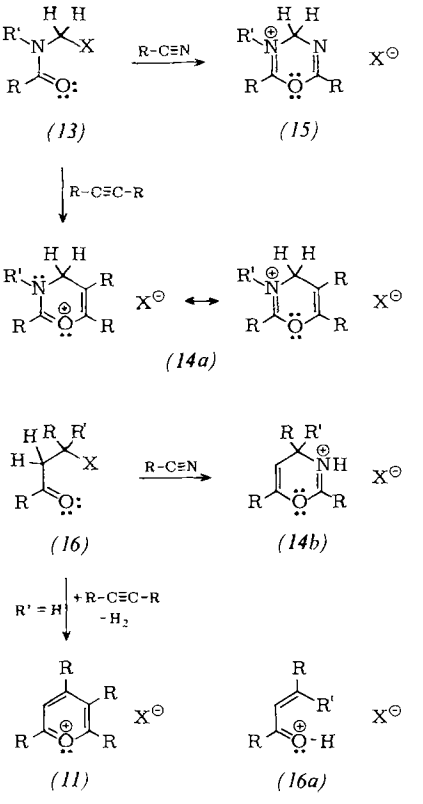
The reactions of the β-chlorovinyl ketones are formally comparable. With acetylenes they lead to pyrylium salts *(11)*[15,22,23], and with nitriles they give moderate yields of 1,3-oxazinium salts *(10)*[19]; the pyrylium salts *(11)* can also be obtained directly from acyl chlorides, acetylenes, and tin(IV) chloride[23].

Though the cycloaddition step in these reactions is reversible and subject to thermodynamic control, the formation of energy-rich vinyl cations from β-chlorovinyl ketones must be regarded as doubtful. IR-spectroscopic findings[20,24] are compatible with the formation of the undoubtedly strongly electrophilic complex *(12)*, which reacts with systems containing triple bonds to give the adducts *(10)* and *(11)*.

The reasons for the fact that numerous Diels-Alder reactions can be catalyzed by Lewis acids[25] are probably similar. Thus an increase in the electrophilic (or nucleophilic, see Section 3) strength of a cycloaddition partner by charge transfer considerably widens the scope of such reactions (see Section 1.2).

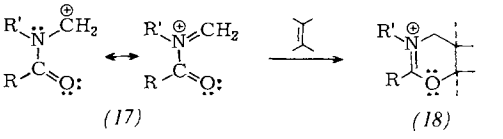
2.1.3. [4⊕+2] Cycloadditions *via (2)*

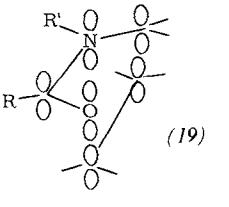
The carbonyl compound *(13)* can be converted into a polar system having the structure *(2)* by loss of the nucleofugal group X; this process is generally facilitated by suitable substitution and by acid catalysis[15,26–28]. Thus *(13)* reacts with acetylenes to give the 4*H*-1,3-oxazinium salts *(14a)*[15,29], and with nitriles to give the 4*H*-1,3,5-oxadiazinium salts *(15)*[30]. The latter reaction is reversible with excess nitrile[31]. The reaction with acetylenes can also be carried out as a multicomponent reaction with acyl chlorides, aldimines, and tin(IV) chloride[29].



Similarly, the pyrylium salts *(11)* are formed from *(16)* and acetylenes *via* unstable dihydropyrylium salts[24,29] by spontaneous dehydrogenation[15,19], and the 4*H*-1,3-oxazinium salts *(14b)* from *(16)* and nitriles by prototropy[26–28]. The polar system *(16a)*, which is structurally related to *(4)*, may be an intermediate in these last reactions.

The orientation in these additions is regiospecific; it corresponds to the rules of electrophilic addition. However, this tells us, *a priori*, nothing about the time sequence of the bond formation in the addition. The *N*-substituted amide *(13)* loses the nucleophilic group X to form the amidomethylium ion *(17)*; *(17)* is a polar system having the structure *(2)*, whose b center is an atom with a lone pair of electrons. In a planar arrangement, the two reactive centers interact *via* π bonds, and the conditions are favorable for a thermally allowed synchronous reaction.





Because of the two hetero atoms and the positive formal charge, however, the reactivity of the amidomethylium ion *(17)* could be changed in such a way that the synchronous action of the two reactivity centers with multiple bonds is overtaken by the two-step electrophilic cycloaddition.

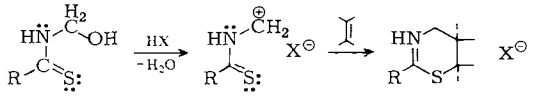
The reaction course was investigated for the cycloaddition of *(17)* to activated and nonactivated olefins, which leads in excellent yields to variously substituted 5,6-dihydro-4*H*-1,3-oxazinium ions *(18)*[32-35]. A two-step course was first deduced from the directional specificity[32]. The *cis* stereospecificity, the weak substituent effect, the inverse addition to methacrylic esters, the formation of a single product on addition to norbornene, and the results of an investigation on the geometry of the transition state in this cycloaddition support the multicenter process[33-35]. According to *Huisgen*[36], however, it is conceivable that the new σ bonds differ in the extent to which they have been formed in the transition state.

The orbital interaction and its importance to the reaction in such unsymmetrical systems has not yet been discussed. However, all the facts are compatible with a $[{}_{\pi}4_s + {}_{\pi}2_s]$ process with *(19)* as the transition state, this being the most probable of several possible[4,12] cyclic transition states.

The addition of chiral amidomethylium ions [*e.g. (17)*, R = C_6H_5—$CH(OCH_3)$] to olefins having no plane of symmetry in the plane of the π bond is a diastereogenic reaction. The determination of the ratio of the diastereoisomers (*e.g.* by NMR spectroscopy) provides information about the kinetic or thermodynamic control of the new σ bonds. Investigations of this kind show that in additions to electron-richer olefins, as even to α-methylstyrene, the kinetically controlled synchronous addition of *(17)* is accompanied by a slow two-step reaction, and that the bond between O and C-6 in the cycloadduct *(18)* is reversibly broken[37].

The synthesis of the oxazinium ions *(18)* can also be carried out as a three-component process by reaction of carboxamides, formaldehyde or formaldehyde derivatives, and olefins in glacial acetic acid/sulfuric acid[35,38-40] or of carbonyl chloride, *N*-alkylaldimine, and olefin in the presence of tin(IV) chloride[35]. The cycloaddition of the amidomethylium ions *(17)*, with R = alkyl and aryl, to 1,3-dienes yields 6-vinyl-substituted oxazinium ions[32,35]; according to *Merten* and *Müller*[41] and to *Petersen*[42], tetrahydropyridines can be prepared with alkoxy-substituted amidomethylium ions [*(17)*, R = alkoxy] by [$2^{\oplus}+4$] cycloaddition (see Section 2.3.1.).

Thioamidomethylium ions *(20)* can be produced *in situ* from hydroxymethyl compounds by acid catalysis and added in a similar manner to olefins to form 5,6-dihydro-4*H*-1,3-thiazinium salts *(21)*[30]. The addition is directionally specific and stereospecific; the yields are lower than in the reaction of amidomethylium ions *(17)*[30].

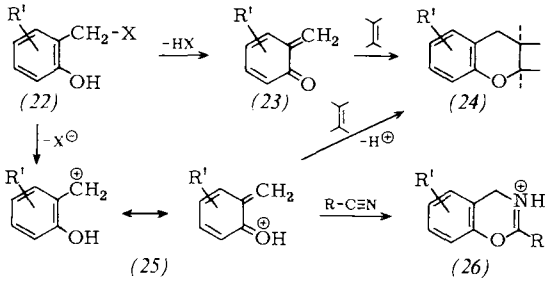


(20) *(21)*

2.1.4. [$4^{\oplus}+2$] Cycloadditions *via (4)*

In these systems the reactive centers are coupled by π-electron resonance, so that conditions are favorable for thermally allowed synchronous reactions.

The reactions of *o*-hydroxybenzyl alcohols, *o*-hydroxybenzylamines, and *o*-hydroxybenzyl halides [*(22)*, X = OH, NR_2, Hal] are particularly interesting. Unstable *o*-quinonemethides *(23)* can be produced *in situ* by thermal cleavage[44-46] or by the action of bases[47], and these react with olefins in a [4 + 2] cycloaddition to give moderate yields of chromans. The [$4^{\oplus}+2$] cycloaddition of the more electrophilic protonated *o*-quinonemethides *(25)* to olefins allows a distinct improvement of the yield[47,48]. Not unexpectedly, the addition is *cis*-stereospecific, and is also directionally specific if the olefin substituents are sufficiently different[48]; the time sequence of the bond formation has not yet been investigated[*].

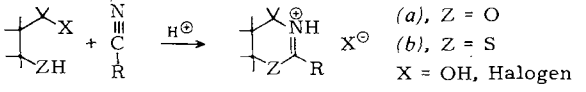


(22) *(23)* *(24)* *(25)* *(26)*

The protonated *o*-quinonemethides *(25)* add smoothly to nitriles to form 4*H*-1,3-benzoxazinium ions *(26)*[19,50] The synthesis of 1,4- and 3,4-dihydroquinazolines from α-chloromethylanilines, nitriles, and tin(IV) chloride[51] is comparable with this reaction.

2.1.5. [$4^{\oplus}+2$] Cycloadditions *via (5)*

The linkage of the reactive centers in the system *(5)* *via* tetragonal centers suggests *a priori* that the formation of the new σ bonds in the cycloaddition should be independent of time. Representative examples are the synthesis of 5,6-dihydro-4*H*-1,3-oxazinium salts *(27a)* from 1,3-diols[52-54] or 3-halopropanols[55] and nitriles by the action of acids, as well as the synthesis of 5,6-dihydro-4*H*-1,3-thiazinium salts *(27b)* from mercapto alcohols and nitriles[55-58] and the synthesis of 6*H*-1,3-thiazines from β-mercapto ketones and nitriles[59] by the action of acids.



(a), Z = O
(b), Z = S
X = OH, Halogen

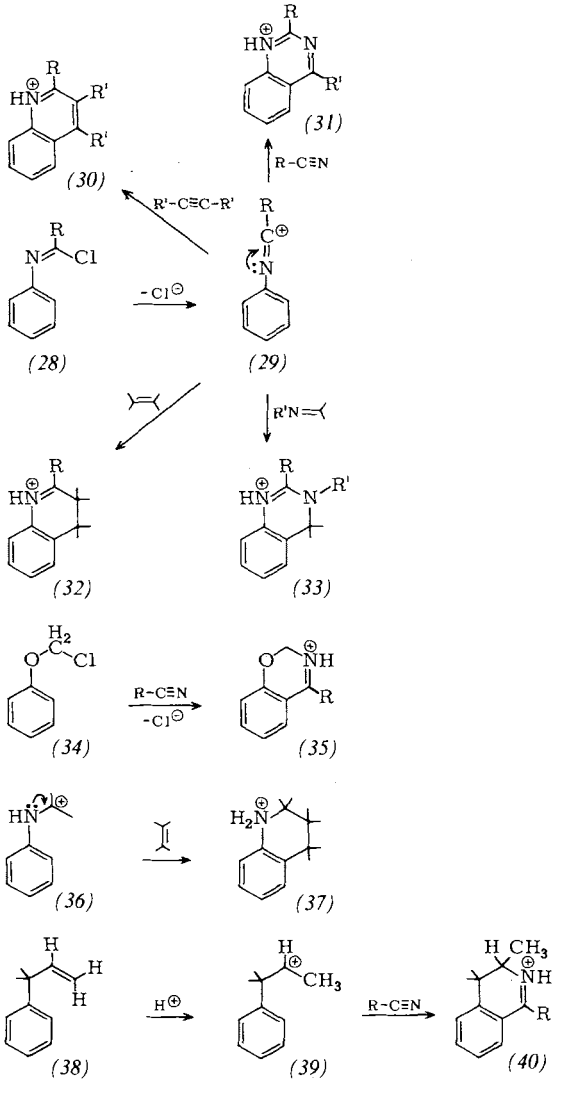
(27)

2.1.6. [$4^{\oplus}+2$] Cycloadditions *via (6)* and *(7)*

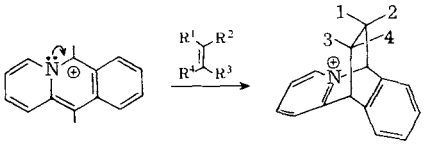
The cycloaddition of the systems *(6)* and *(7)* to multiple bonds leads to a formal positive charge at the c center; the resulting energy-rich intermediate is then often stabilized by loss of a positive residue.

[*] Enol ethers [47] and enamines [49] undergo [4 + 2] cycloadditions.

N-Arylimidoyl chlorides *(28)* can thus be converted with Lewis acids into isolable, resonance-stabilized cations *(29)*, which undergo cycloaddition with alkynes, nitriles, olefins, and electron-deficient imines to give quinolines *(30)*[60], quinazolines *(31)*[61,62], 3,4-dihydroquinolines *(32)*[19], and 3,4-dihydroquinazolines *(33)*[1] in good yields. The reaction of α-chloromethyl phenyl ether *(34)* with nitriles similarly leads to 2*H*-1,3-benzoxazines *(35)*[19], the reactions of the *N*-arylimonium ions *(36)* with olefins to tetrahydroquinolines *(37)*[63], and the reaction of allylaromatic compounds *(38)*, and of many starting compounds that give arylethyl cations *(39)* under the action of acids, with nitriles to 3,4-dihydroisoquinolines *(40)*[64–69]. Comparable reactions can also be carried out with unsaturated aliphatic systems[69]. The stereochemistry of the olefin reactions mentioned above has not yet been investigated. For simplicity, the products are shown in the protonated form.



The cycloadditions of acridizinium systems *(41)* to olefins to form the adducts *(42)–(45)*[70–73] should also be mentioned. The polar 1,4-system *(41)* is formally identical with *(36)* in the occupation of the centers. On thermodynamic grounds, however, the reaction stops at the cycloadduct stage in this case, whereas the intermediate adduct in the reaction of *(36)* with olefins undergoes cleavage of a C—H bond to give the system *(37)*.



(41) *(42)–(45)*

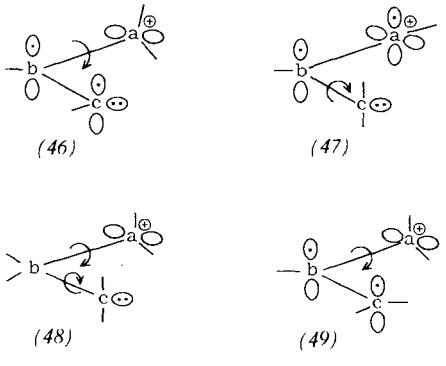
	1	2	3	4
(42)	R^1	R^2	R^3	R^4
(43)	R^2	R^1	R^4	R^3
(44)	R^1	R^2	R^4	R^3
(45)	R^2	R^1	R^3	R^4

The acridizinium ion *(41)* is a polar system having the structure *(7)*, with a lone pair of electrons on the atom at the b center; the conditions are therefore favorable for a synchronous cycloaddition (see Section 2.1.1.). The addition is substantially direction-specific, but generally only diastereoselective (the diastereoisomers *(42)* and *(43)* are formed in different quantities). Moreover, the adducts *(44)* and *(45)* of the olefin rotamers are formed on addition to electron-deficient olefins; this points to a two-step process[71]. Whether this is also true of electron-richer olefins remains to be answered by further investigations.

(41) also reacts with acetylene derivatives[74]; moreover, analogous adducts are formed from isoquinolinium salts[75], 7a- and 11a-azoniabenz[*a*]anthracene[75,76], 9a-azoniabenzo[*b*]triphenylene[76], 5a-azonianaphthacene[76] and 4a, 8a-diazoniapentaphene[76].

2.2. [3⊕ + 2] and [3⊕ + 4] Cycloadditions

Polar 1,3 systems occur chiefly in the forms *(46)–(49)*.



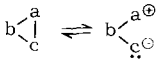
(46) *(47)*

(48) *(49)*

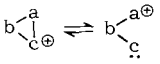
The two centers a and c will react independently of each other in the systems *(46)–(48)*. The orbitals available on a and c for the formation of the new σ bonds are separated by a tetragonal center in *(48)*, and no low-energy mesomeric 4π system is to be expected from *(46)* and *(47)* even on suitable rotation about single bonds (see Section 2.1.1.); a 4π system of this type could be present in *(48)* if b is an atom having a lone pair of electrons. Mesomeric 2π allyl cation systems are present in *(46)* and partic-

ularly in *(49)*, so that synchronous supra-suprafacial additions to 4π systems should be possible. Some examples of the systems *(46)*, *(48)*, and *(49)* are mentioned below.

A preferred method for the production of such systems is the cleavage of three-membered rings with acids. Thus the valence tautomerism described by *Greene* and *Hecht*[11] between the three-membered rings and the corresponding 1,3-dipoles is strongly dependent on the groups representing a, b, and c. In the case of the three-membered ring cations, however, there is generally a distinct preference for the open-chain polar 1,3 system.



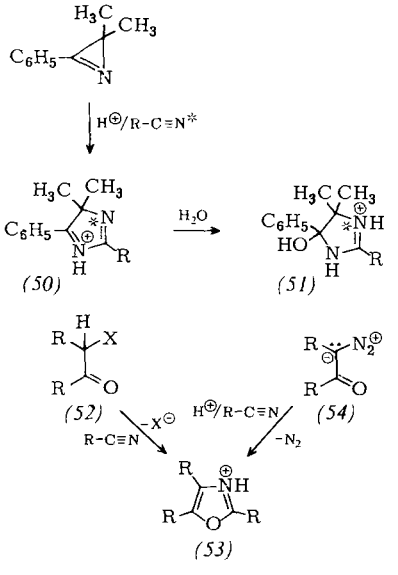
(8)



(9)

2.2.1. [3⊕+2] Cycloadditions *via (46)*

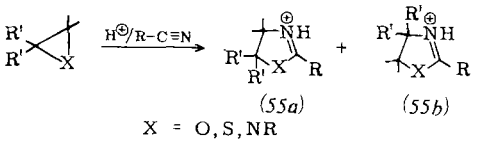
Azirines add to nitriles in acidic solution. The imidazolium ions *(50)* are formed as intermediates, and have been isolated as water adducts *(51)*[77]. The position of the cleavage of the azirine ring has been established by labeling of the nitrile nitrogen atom.



Oxazolium ions *(53)* are readily obtained by reaction of α-halo ketones *(52)*, X = halogen, with nitriles in the presence of Lewis acids[78,79]. α-Hydroxy ketones *(52)*, X = OH[80], and α-diazo ketones *(54)*[19] react similarly in the presence of protonic acids. On the other hand, the 1,3 dipole formed from *(54)* generally adds to nitriles only in very modest yields[81]. Oxazolones are obtained from α-hydroxy carboxylic acids[82–84] or cyclopropenylcarboxylic acids[85] with nitriles.

2.2.2. [3⊕+2] Cycloadditions *via (48)*

Epoxides are converted into the oxazolinium ions *(55)*, X = O, in the presence of nitriles under the action of acids[77,86,87]. Similarly, episulfides are converted into thiazolinium ions *(55)*, X = S[88,89]. The episulfide ring cleavage takes place stereospecifically with inversion; it may be assumed, therefore, that neither a free carbenium ion nor an ion pair occurs as an intermediate in the ring cleavage. Intermediates of this type are, however, formed in the analogous reaction of allylthiols or 2-mercapto alcohols in the presence to acids. Addition to nitriles also leads to thiazolinium ions[90,91]. The acid-catalyzed additions of epoxides to ketones, aldehydes, isocyanates, SO_2, SO_3, and CO_2[92], for example, may also be included in this group.

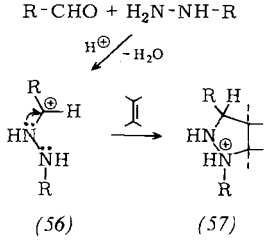


(55a) *(55b)*

X = O, S, NR

Aziridines are converted by protonation or alkylation into aziridinium salts, which readily undergo ring cleavage[93]. The resulting reactive intermediates add to nitriles to form imidazolinium ions *(55)*, X = NH or NR[77,94–97] and to aldehydes and ketones to form oxazolidinium ions[93,96,98–100]. The two new σ bonds are formed independently of each other in two steps[93].

The described ring cleavage of aziridines, epoxides, and episulfides always leads to the more stable carbenium ion as an intermediate[102]; the isomers *(55a)* and *(55b)* are formed together if the stabilities of the corresponding intermediates are comparable.

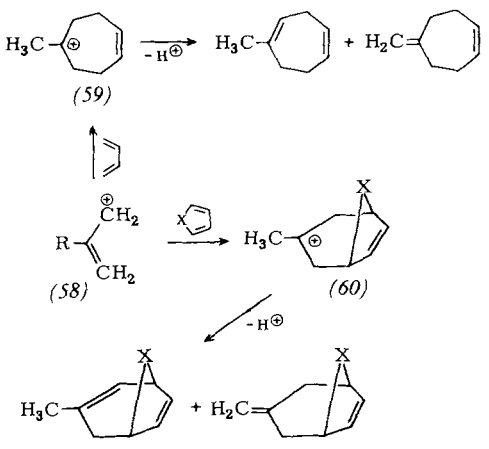


(56) *(57)*

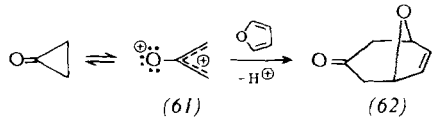
A particularly interesting [3⊕+2] cycloaddition was described by *Hesse*[101]. The *N*-aminoimonium ions *(56)* formed as intermediates from aldehydes and hydrazines can add to olefins with formation of pyrazolidinium ions *(57)*. The polar 1,3 system *(56)* may undergo a synchronous $[_\pi 4_s + _\pi 2_s]$ cycloaddition with olefins because of the nonbonding pair of electrons on the b center; so far as we know, however, the course of the reaction has not yet been investigated.

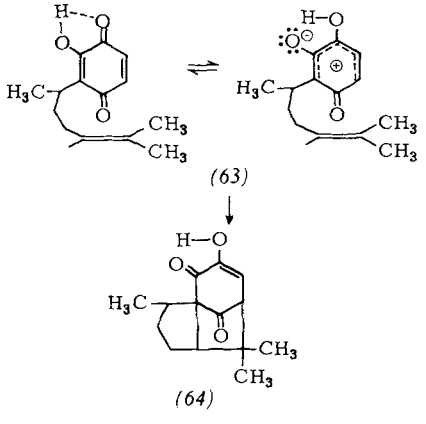
2.2.3. [3⊕+4] Cycloadditions *via (49)*

Allyl cations *(58)* are ideal examples of polar systems having the structure *(49)*, since the interaction between a and c is not disturbed by differences in the electronegativities of the centers. The conditions are therefore favorable for a synchronous addition to dienes in the form of a $[_\pi 4_s + _\pi 2_s]$ cycloaddition. 2-Methylallyl cations *(58)*, R = CH_3, can in fact add *cis*-specifically to open-chain and cyclic conjugated dienes. The reaction leads *via* positively charged cycloheptenes *(59)* and branched cycloheptenes *(60)* by deprotonation to cycloheptadienes and methylenecycloheptenes or the corresponding bridged compounds[103–106].



Cyclopropanones react with conjugated dienes, *e.g.* furan, to form adducts of the type *(62)*[107-109]. Possibly the cyclopropanone exists in equilibrium with a dipolar species *(61)*. *(61)* could react as a 2π-electron system and combine with dienes in a $[_\pi 4_s + _\pi 2_s]$-process[4]. This interpretation of the reaction course by *Woodward* and *Hoffmann*[4] presupposes the detection of this ring cleavage; a $[_\pi 4_s + _\sigma 2_s]$-process, without prior opening of the cyclopropane σ bond, could also explain the reaction.

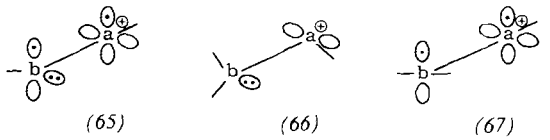




The formulation of polar systems by localization of π electrons of uncharged π systems would suggest that the formation of the pipitzols *(64)* from perezone *(63)*[110] involves a $[5^{\oplus} + 2]$ cycloaddition[4], and ultimately leads to the classification of the addition of ketenes to 2π systems as the cycloaddition of a vinyl cation[4,111] to a 2π system (see Section 2.3).

2.3. $[2^{\oplus} + 2]$ and $[2^{\oplus} + 4]$ Cycloadditions

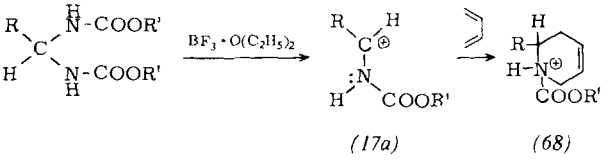
Polar 1,2 systems can occur mainly in the forms *(65)*–*(67)*.



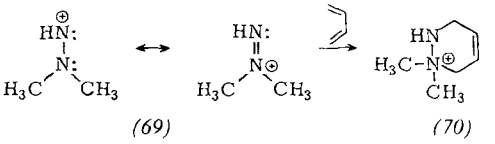
The two reactive centers a and b in the systems *(65)* and *(66)* interact *via* 2π electrons, so that with 1,3-dienes $[_\pi 4_s + _\pi 2_s]$ processes are possible. No such interaction occurs in the system *(67)*. Synchronous processes are possible, if at all, only with the aid of the π bond between a and b, *e.g.* as $[_\pi 2_a + _\pi 2_s]$ processes[4,109-111]. Examples of the systems *(66)* and *(67)* are given below.

2.3.1. $[2^{\oplus} + 4]$ Cycloadditions *via (66)*

Alkoxycarbonylamidomethylium ions *(17a)*, as was mentioned earlier (see Section 2.1.3), add *cis*-stereospecifically to conjugated dienes to form tetrahydropyridines *(68)*[40,41]. This reaction was successfully used by *Huisman*[112] for the synthesis of azasteroids.

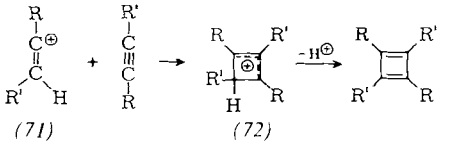


The azalog of *(17a)* behaves similarly. Thus the diazenium ion *(69)* reacts smoothly with conjugated dienes to form tetrahydropyridazines *(70)*[113,114]. The reaction mechanism has not yet been verified for either reaction.



2.3.2. $[2^{\oplus} + 2]$ Cycloadditions *via (67)*

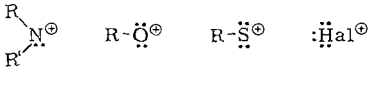
The most important example here is the formation of cyclobutenyl cations *(72)* from vinyl cations *(71)* and acetylene derivatives[117-119], which led to the synthesis of the first stable cyclobutadiene[118]. The discussion of the reaction mechanism is probably not yet closed[4,111]. The ketene-olefin addition (see Section 2.2.3) should not be included in this reaction scheme because of formal considerations.



Whether [2+2] cycloadditions catalyzed by transition metal ions[115] and a number of other reactions[*] should be mentioned as $[2^{\oplus} + 2]$ cycloadditions must be left for further investigations to decide.

2.4. $[1^{\oplus} + 2]$ and $[1^{\oplus} + 4]$ Cycloadditions

Polar 1,1 systems capable of cycloaddition consist of positively charged centers with a non-bonding occupied and an unoccupied orbital. Examples of such systems are the following cations:



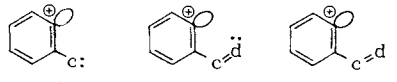
[*] See *e.g.* the formation of pyridylcyclobutanes by acid-catalyzed cycloaddition of enamines to vinylpyridines[116].

Numerous groups having a corresponding electronic structure are also to be found among the transition metal ions.

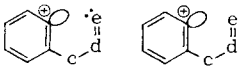
Though $[1^{\oplus}+2]$ and $[1^{\oplus}+4]$ cycloadditions of these positively charged sextet centers to 2π and conjugated 4π systems are generally accepted[120], details are still under discussion[121-124]. Two-electron three-center bonds between 2π systems and the unoccupied orbitals of protons or carbenium ions (with formation of non-classical carbonium ions) may be included here[125,126].

2.5. Cycloadditions *via* Phenyl Cations

The ionic components capable of cycloaddition that were mentioned in Sections 2.1 to 2.4 have an alkyl cation or vinyl cation structure or a comparable structure on the a center. Thus there still remains the questions of phenyl cations capable of cycloaddition. According to the structural requirements discussed above for polar systems they should have *e.g.* the structures *(73)–(77)*.



(73) [≙*(47)*] *(74)* [≙*(1)*] *(75)* [≙*(6)*]



(76) *(77)*

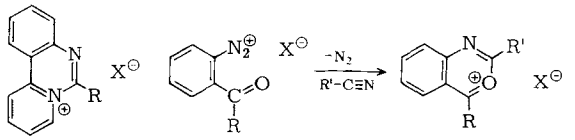
Cationic species of this nature can be formally produced by thermolysis of benzenediazonium ions, since the thermal decomposition of diazonium ions is the prototype of the aromatic S_N1 reaction[127-129].

Investigations of this type are significant for the discussion of the interaction of orbitals that are separated by one or more σ bonds and whose preferred direction is in the plane of the σ skeleton[12,13]. Some examples will be given here to allow the discussion of the variation of the number of centers of polar systems having the same structure and charge.

Thus cycloadducts are formed *via* the intermediate *(74)* on thermolysis of 2-(α-pyridyl)benzenediazonium salts in nitriles, which serve both as reactants and as the reaction medium. Derivatives of pyrido[1,2-*c*]quinazoline *(78)*[13,43,130] are formed in excellent yields. Instead of a CN group, a CO double bond *ortho* to the diazonium group can act as a functional group. Thus the analogous reaction of the *o*-carbonyl-substituted benzenediazonium salts *(79a)–(79d)* yields benzoxazinium salts *(80)*[13,130,131].

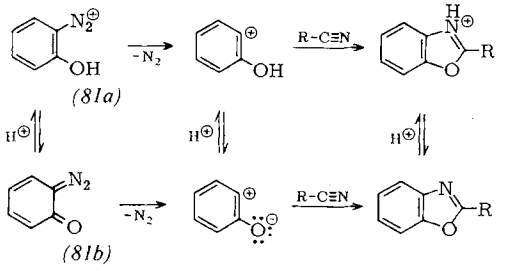
The *o*-carboxybenzenediazonium salt *(79e)* behaves quite differently from the corresponding acid *(79d)*[13,131]. This has a parallel in the behavior of the *o*-hydroxybenzenediazonium ion *(81a)* and the corresponding diazo ketone *(81b)*[130]. Whereas the thermolysis of *(81b)* in nitriles generally leads in modest yields to benzoxazoles in accordance with the 1,3-dipolar cycloaddition scheme[81], the reaction of *(81a)* can be directed *via* an intermediate of the type *(73)* to give benzoxazolium ions in good yields[130].

The two nitrogen-free species thus react differently. The unprotonated form, despite the fact that a dipolar structure can be formulated[81], reacts more slowly with the nitrile than to form competing products; the protonated form, on the other hand, reacts faster with the nitrile (for α-diazo ketones, see Section 2.2.1).



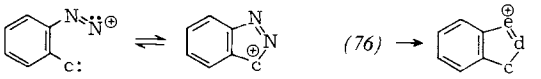
(78) *(79)* *(80)*

(a), R = Aryl; *(b)*, R = Alkyl; *(c)*, R = NR_2; *(d)*, R = OH; *(e)*, R = $O^{\ominus}$



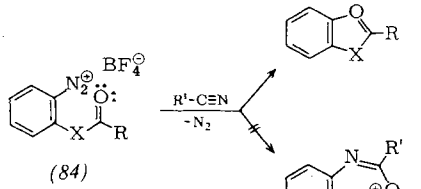
(81a) *(81b)*

All investigations have shown that the diazonium ion must be present in the free state. Intramolecular cyclizations with *ortho* substituents as in equilibrium *(82a)*⇌*(82b)* interfere with the cycloadduct formation after the liberation of nitrogen (free-radical intermediates presumably occur[132]). Because of the low electrophilic strength of the diazonium group, therefore, the best results are obtained in a weakly acidic medium[19].



(82a) *(82b)* *(83)*

An increase in the number of ring atoms, as in *(76)* and *(77)*, suppresses the intramolecular cyclization of the diazonium compound in accordance with *(82a)*⇌*(82b)* on steric grounds, but facilitates the intramolecular reaction of the phenyl cation *(76)* to form the system *(83)*[130]. Thus in the thermolysis of the diazonium salt *(84)* in nitriles, the reaction leading to the five-membered heterocycle is accelerated at least to such a degree that the intermolecular reaction with a nitrile to form the seven-membered heterocycle is no longer important[130].

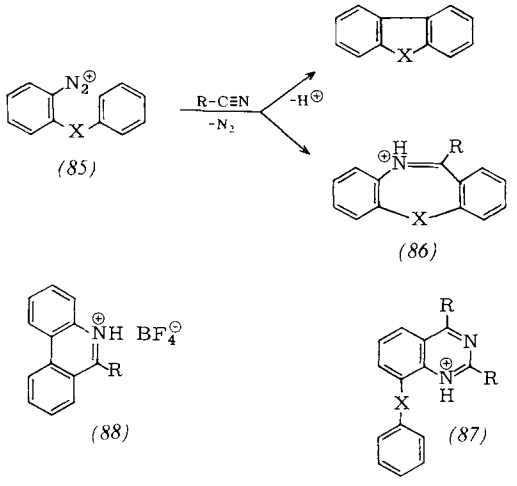


(84)

(a), X = N-CH_3, R = C_6H_5
(b), X = CH_2, R = OH

If the reactivity of the e center of *(76)* is reduced by transition to systems having the structure *(77)*, the intramolecular reaction is retarded.

This case is found in the thermolysis of diazonium ions having the structure *(85)*[13,130,133]. The main products are the morphanthridines *(86)*, X=CH_2, dibenz[*b*,*f*][1,4]oxazepines *(86)*, X=O, and dibenzo[*b*,*f*][1,4]thiazepines *(86)*, X=S. However, the products of the intramolecular reaction are also formed in small quantities by a Pschorr ring closure, as well as the quinazolines *(87)* by twofold reaction with the nitrile. If there are no functional groups *ortho* to the diazonium group, *(87)* becomes the main product[16]. The synthesis of phenanthridines *(88)* from *o*-phenylbenzenediazonium salts[13,133-135], which is derived from system *(75)*, proceeds without appreciable by-products, since the intramolecular reaction of the intermediate would lead to energy-rich four-membered ring systems. *(85)*–*(87)* are shown as cations for the sake of simplicity.



(85) *(86)* *(88)* *(87)*

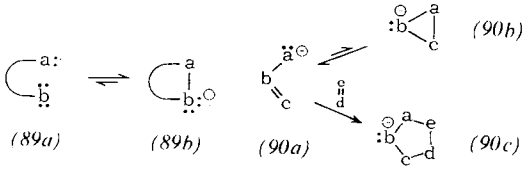
In addition to nitriles, isocyanides can also be successfully used as addition partners for ionic components of this type, and [4⊕+1] and [5⊕+1]-cycloadducts are obtained[13,136].

3. Anionic Polar Cycloadditions

Anionic intermediates that are capable of cycloaddition are much less known than cationic intermediates. There may be two reasons for this:

1. Systematic investigations on reactions of this type have only recently been carried out[137-140].

2. Systems with negative charges on the reactive center a and a sextet of electrons on the second reactive center b, as in *(89a)*, probably change irreversibly into the cyclic form *(89b)*. The remaining polar intermediates capable

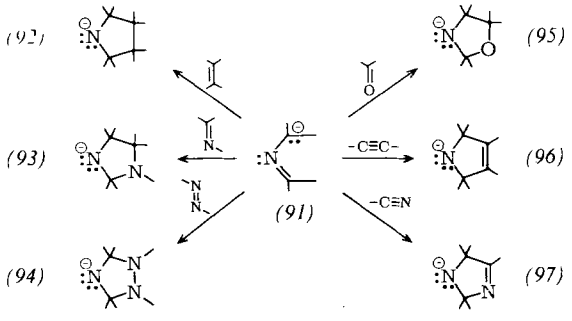


(89a) *(89b)* *(90a)* *(90b)* *(90c)*

of cycloaddition are thus mainly systems having the structure *(90a)* with a multiple bond between b and c. On intramolecular cyclization to form *(90b)* or on cycloaddition to form *(90c)*, the center b accepts a lone pair of electrons and also the negative charge. If b is more electronegative than a or if the tendency for the π bond in the addition partner d=e to disappear is great, the cycloaddition will be favored on thermodynamic grounds.

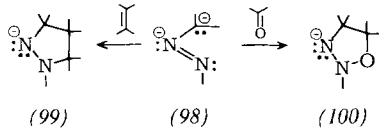
3.1. [3⊖+2] Cycloadditions

Outstanding examples in accordance with the scheme *(90a)*→*(90c)* are the cycloadditions of the 2-azallyl[137,139,140] and 1,2-diazallyl anions[138] *(91)* and *(98)* to 2π systems by *Kauffmann*[137-140]. Thus *(91)* can add smoothly to olefins, azomethines, azo compounds, ketones, acetylenes, and nitriles, the electronegative nitrogen atom of *(91)* taking over the negative charge. The corresponding five-membered heterocycles can be obtained from the anions *(92)*–*(97)*. The diazallyl anion *(98)* similarly adds to olefins and ketones with formation of the five-membered heterocycles *(99)* and *(100)* (shown as anions) respectively. The two reactive centers in the allyl anion system interact with each other *via* π electrons, so that the observed stereospecific *cis*-addition is not surprising and a [$_{\pi}4_s+_{\pi}2_s$] process seems likely.



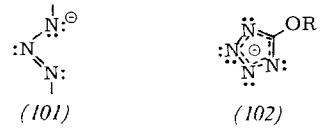
(92) *(93)* *(94)* *(91)* *(95)* *(96)* *(97)*

The localization of the negative charge on a more electronegative atom suggests that *(98)* should have less tendency than *(91)* to undergo addition; the nucleophilicity of the reactive component is reduced as a whole[139]. Cycloadditions to the even more inert triazallyl anion *(101)* are unknown.



(99) *(98)* *(100)*

Strong stabilization of the cycloadduct by delocalization of the negative charge occurs on addition of the azide ion to cyanate to form tetrazolyl anions *(102)*[141]. The lower nucleophilicity of the azide ion is compensated for by the energy gain on formation of the heteroaromatic compound.

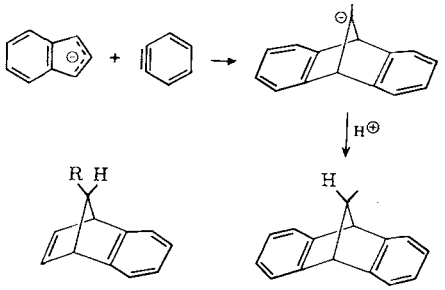


(101) *(102)*

The stabilization of a cycloadduct anion by localization of the negative charge on a more electronegative atom or by delocalization is also responsible for the addition of transition metal complex anions *e.g.* to olefins[142].

Questions of this nature are of minor importance in the case of particularly reactive addition partners. The energy for the localization of the negative charge on a less favored center is supplied by the reactive addition partner.

Thus allyl anions (or their metal compounds as anionoids) such as the indenyl anion and the cyclopentadienyl anion add smoothly to dehydrobenzene to form dibenzonorbornadiene *(103)*[142-144] or benzonorbornadiene *(104)*[145].



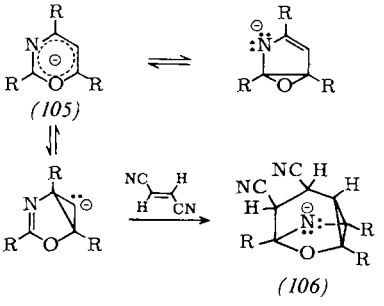
(104) *(103)*

3.2. $[4^{\ominus}+2]$ Cycloadditions

Cycloadditions of anionic components having more than three centers are practically unknown, though there are in principle many possibilities. This will be illustrated by two examples of $[4^{\ominus}+2]$ cycloadditions.

Anionic intermediates formed *in situ* from acetylide ions and nitriles give pyridines or pyrimidines on addition of a further molecule of acetylene or nitrile[146].

Heterocyclic 8π systems having the structure *(105)* are electronically destabilized[147]; they can escape from this state by valence tautomerism. Cycloaddition reactions may also be included in this process; thus *(105)* reacts with fumarodinitrile *via* the anion to give the heterotricycle *(106)* together with other products[19].



(105) *(106)*

4. Closing Remarks

The survey of polar cycloadditions has shown that besides carbocycles, very many heterocycles can be synthesized from ionic components by this reaction principle. Some of these ionic components can be isolated, while sometimes they occur in the form of reactive intermediates. In the first case the driving force for the reaction lies in the particular stability of the end products, and in the second case in the enhanced reactivity of the intermediates.

The number of unused reaction possibilities is undoubtedly very large, and the number of mechanistic questions that have not been clarified is equally large. This latter statement refers both to the structure of the polar intermediates and to the nature of the addition to multiple-bond systems. The clarification of these mechanistic questions is particularly interesting in that boundary cases between synchronous and non-synchronous formation of the new σ bonds are very often found. Moreover, some of these polar systems are good examples for the investigation of orbital interaction *via* σ bonds[12,13]

There are two main characteristics that distinguish the polar from the non-polar and dipolar cycloaddition components:

1. The high electrophilic or nucleophilic strength makes them ideal cycloaddition partners for hetero-multiple bonds and all kinds of olefins.

2. The tendency toward irreversible intramolecular cyclization is much weaker than in the dipolar cycloaddition components.

The importance of cycloadditions with polar components, therefore, is probably no less than that of cycloadditions with uncharged and with dipolar components.

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Spectroscopic Properties of Organic Azo Compounds

By Hermann Rau[*]

Azo compounds are characterized by a low-energy $^1(n,\pi^*)$ electronic state, which gives rise to a weak band at long wavelengths in the absorption spectrum. Coupling of this state with other low-lying molecular states is responsible for the high intensity of the "azo band" compared to other forbidden transitions, for its lack of vibrational structure, and for the inability of nearly all organic azo compounds to fluoresce.

1. Introduction

Although the azo group —N=N— has given its name to a large class of organic dyes, spectroscopists have shown comparatively little interest in this atomic grouping. The reason may lie in the effects of two rules characterizing the spectroscopic behavior of the azo compounds:

1. the azo group has a "structure-destroying effect"[1];

2. azo compounds do not emit.

The information that can be gleaned from absorption and emission spectra is therefore very limited.

By searching for exceptions to these rules, however, it is possible to clarify the spectroscopic properties in molecular terms. This involves the extensive use of theoretical considerations, and because of the shortage of experimental data the conclusions are necessarily somewhat speculative.

Only one field of the spectroscopy of azo compounds has been investigated in depth, *i.e.* their photochemistry, in particular the *cis-trans* isomerization of aromatic azo compounds and the photodecomposition of aliphatic azo compounds. These two processes will be considered in

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the following discussion only insofar as they are relevant to the coupling of the lowest excited states.

2. Fundamentals

2.1. Molecular States

2.1.1. Pure Stationary States

It is known from spectroscopic experiments that a molecular system can absorb or emit radiation only in characteristic quanta $h\nu$, and that in so doing it passes from one energy state into another (Fig. 1a). The spin state must remain the same in this process ($S_0 \rightarrow S_1$), any change in multiplicity ($S_0 \rightarrow T_1$) being forbidden.

This leads to an energy level diagram as shown in Figure 1b in which electronic states are combined with vibrational states $v_0, v_1, v_2 \ldots$, the individual properties of the states being retained.

2.1.3. Nonstationary States

The independence of the coordinates is really only an approximation, which is satisfied to a greater or lesser degree by any real system. Electronic and vibrational states may be coupled among themselves and with one another.

Since the molecular states have the properties of oscillators, interaction between two states leads to two new states, one of higher energy and another of lower energy (Fig. 1c). The splitting ΔE depends on the extent of coupling.

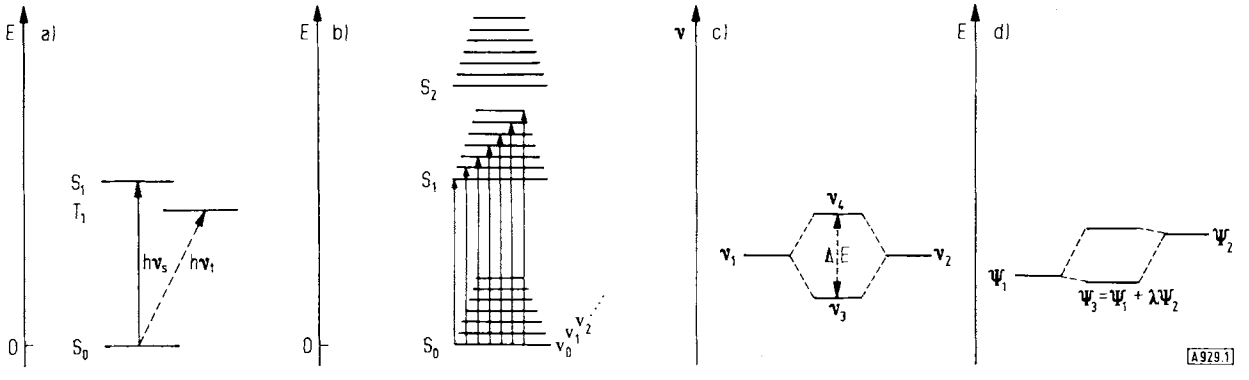


Fig. 1. a) Stationary states; b) Born-Oppenheimer states; c) coupled classical oscillators; d) coupled molecular states.

These states are characterized in that the molecular system does not spend only a short time in them. They are described by standing matter waves, the wave function containing all the information about the state. The spectroscopist is interested in energy, symmetry, and lifetime. A state in which the molecule remains is a pure stationary state.

2.1.2. Quasistationary States

States observed by spectroscopic means cannot be pure stationary states, for spectroscopy registers only transitions. However, the states that can be detected spectroscopically are normally so long-lived that they may be regarded as quasistationary and described by a single wave function.

The Born-Oppenheimer (BO) functions are particularly suitable for describing such states. In the BO approximation the internal coordinates of the molecule are resolved into three independent sets corresponding to electronic motion, vibration, and rotation. For molecules in solution, the rotational structure can be observed only in very rare cases; we shall therefore disregard rotation. The complete function of the vibronic state can then be represented in the BO approximation as the product of the electronic and vibrational functions.

$$\psi = \theta(r,q) \cdot \varphi(q) \qquad (1)$$

where r is the set of electronic coordinates and q the set of vibrational coordinates.

In wave-mechanical formalism, coupled states are described by mixing of wave functions (Fig. 1d):

$$\psi = \psi_1 + \lambda\psi_2 = \psi_1 + \frac{\int \psi_1 \mathbf{V} \psi_2 d\tau}{E_1 - E_2} \psi_2 \qquad (2)$$

The mixing coefficient λ is the ratio of the coupling energy between the states ψ_1 and ψ_2 under the interaction $\mathbf{V}$ to the energy difference $E_2 - E_1$. The BO approximation is valid as long as $\lambda \ll 1$.

Another property of coupled states can be illustrated by the behavior of two identical coupled pendulums. If one pendulum is set in motion, the other soon starts to swing, and takes over the energy of motion to such a degree that the first pendulum comes to rest, whereupon the process starts anew with the roles reversed. A molecular system moves to and fro between coupled states, so that the individual state is no longer stationary.

The time τ_p required by the system to return to a certain state depends on the intensity of coupling and on the complexity of the system. The weaker the coupling and the greater the number of coupled states, the longer the system will take to return to its original state, *i.e.* the greater is τ_p[12].

2.2. The Azo Group

The azo group consists of two nitrogen atoms linked by a double bond, each of these atoms carrying a non-bonding

pair of electrons. The chemical and photochemical stability of azo compounds increases with increasing resonance and inductive interaction with the rest of the molecule[3]. Azo compounds are characterized spectroscopically by a low-energy $^1(n,\pi^*)$ state, which is manifested as a weak absorption band at long wavelengths (*e.g.* Fig. 2).

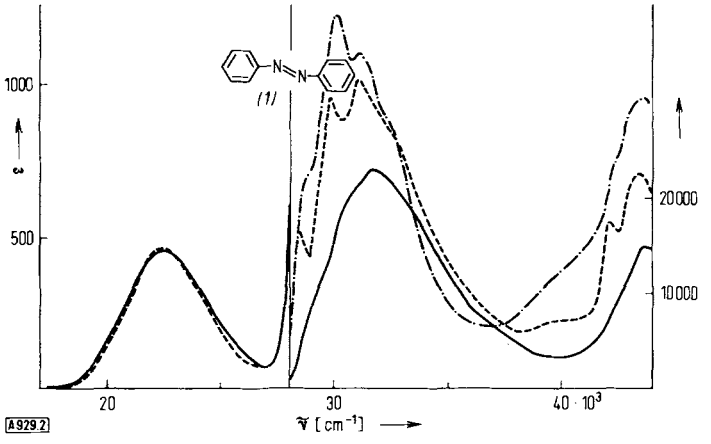
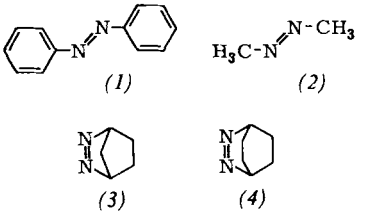


Fig. 2. Absorption of *trans*-azobenzene in methylcyclohexane/isopentane (3:1): ——— at room temperature, – – – – at 77 °K; –·–·– in polyethylene film at room temperature.

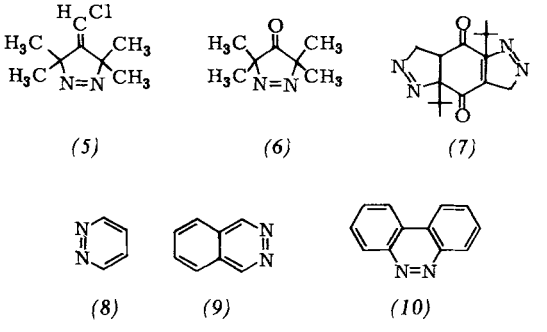
The bond lengths in the azo group are approximately equal in aromatic and in aliphatic azo compounds. The N=N distance is 1.23 Å in azobenzene *(1)*[4] and in azomethane *(2)*[5], and the length of the N—C bond is 1.41 Å in *trans*-azobenzene[6], 1.46 Å in *cis*-azobenzene[7], and 1.47 Å in azomethane[5] (this is practically the length of a resonance-free C—N bond[8]).



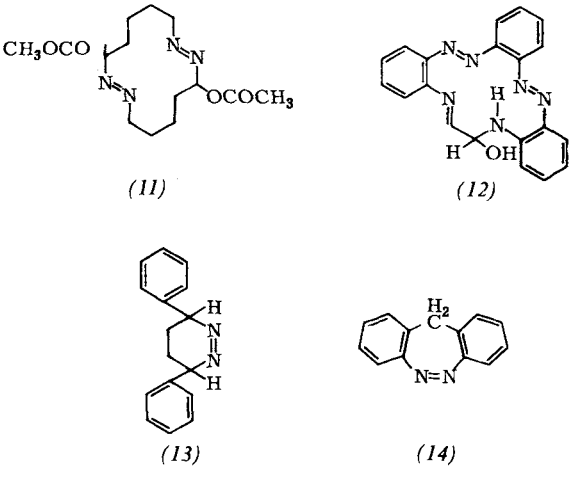
The bond angles at the nitrogen atom are close to 120°[5,6]. This geometry results in *cis-trans* isomerism (cf. *(1)* and *(2)* with *(3)* and *(4)*). The *trans* form is always the more stable of the two isomers. In the case of azobenzene, the energy difference is 12 kcal/mol[9] and the activation energy for the *cis-trans* transition is 23 kcal/mol in solution[10] and 31 kcal/mol in the solid[11], so that the two isomers can be separated at room temperature. For azomethane, this is possible only at low temperatures[12]. Aromatic *cis* azo compounds cannot be planar because of the steric hindrance of the *o*-hydrogen atoms. *cis*-Azobenzene has a planar azo group, but the phenyl rings are parallel to each other and are twisted by 56° out of the plane of the azo group[7].

The azo group in the *cis* configuration can also be part of an aliphatic or aromatic ring system, as in 2,3-diazabicyclo[2.2.1]-2-heptene *(3)*, the corresponding diazabicyclooctene *(4)*, pyrazolines such as *(5)*, *(6)*, and *(7)*, or *o*-diazines such as pyridazine *(8)*, phthalazine *(9)*, or benzo[*c*]cinnoline *(10)*.

These compounds naturally cannot isomerize. Only a few molecules are known which contain a *trans* azo group



in a ring system (*e.g.* *(11)*[13] and *(12)*[14]), and only few spectroscopic data are presently available for the cyclic *trans* azo compounds.



An important factor in the spectroscopy of *cis* and *trans* azo compounds is that they belong to different symmetry groups; the *cis* compounds have C_{2v} symmetry and the *trans* compounds C_{2h}. For aliphatic azo compounds, one need only consider the local symmetry[15] (*e.g.* for *(3)*).

3. Spectral Characteristics of Azo Compounds

3.1. Position of the n→π* Band in the Absorption Spectrum

The position of the n→π* band depends on the groups attached to either end of the azo group[3]. It appears at about 28000 cm^{-1} for aliphatic azo compounds (Table 1) and at 22000 to 23000 cm^{-1} for the aromatic representatives. Surprisingly, the position of the n→π* band is practically unaffected by substitution in aromatic azo compounds, whereas the π→π* bands in the spectrum are shifted considerably (Table 2). This is particularly noticeable for the *trans* diarylazo compounds in Table 3.

Table 1. $n \rightarrow \pi^*$ bands and fluorescence yields of aliphatic azo compounds.

Compound	$\tilde{\nu}_{max}$ [cm^{-1}]	ε_{max}	Structure	Yield [%]	Ref.
trans-$CH_3N{=}NCH_3$	28000	13	none	0	[16,12]
trans-$(CH_3)_2CHN{=}NCH(CH_3)_2$	28000	17	none		[17]
trans-$(CH_3)_3CN{=}N{-}CH(OCOCH_3)(CH(CH_3)_2)$	28000	19	none	0	[18]
(11)	28000	60	77°K: weak	0	[19]
cis-$CH_3N{=}NCH_3$	28400	240	none		[12]
(4)	27000	150	sharp	0.55	[20]
(3)	29500	400	sharp	0.15	[20]
(5)	31000	280	weak	0.01	[18]
(6)	28000	250	none	0	[18]
(7)	30500		weak	≈0.01	[18]
3,5-Diphenylpyrazoline	30500	290			[21]
(13)	25900	770			[19]

Table 2. Spectra of substituted *trans*-azobenzenes *p*-R—$C_6H_4N{=}NC_6H_5$.

R	$n \rightarrow \pi^*$-band $\tilde{\nu}_{max}$ [cm^{-1}]	log ε_{max}	long-wave $\pi \rightarrow \pi^*$-band $\tilde{\nu}_{max}$ [cm^{-1}]	log ε_{max}	Ref.
H	22300	2.61	31600	4.35	[22]
$N(CH_3)_3I$	22500	2.71	31600	4.3	[23]
CH_3	22200	2.83	30000	4.37	[24]
OCH_3	22500	2.8	29000	4.31	[25]
NO_2	22000	2.83	30000	4.35	[17]
$N(CH_3)_2$	21500 [a]	—	24500	4.36	[25]
$N{=}NC_6H_5$	22000	3.4	27900	4.6	[26]

[a] Calculated.

Table 3. Spectra of *trans*-diarylazo compounds, after [27].

Compound	$n \rightarrow \pi^*$-band $\tilde{\nu}_{max}$ [cm^{-1}]	log ε_{max}	1st $\pi \rightarrow \pi^*$-band $\tilde{\nu}_{0-0}$ [cm^{-1}]	$\tilde{\nu}_{max}$ [cm^{-1}]	log ε_{max}
Ph-N=N-Ph	22500	2.65	28500	31500	4.35
Ph-N=N-1-Napht	22100	2.95	26000	27000	4.08
Ph-N=N-2-Napht	22400	2.96	26000	27000 [a]	3.8 [a]
1-Napht-N=N-1-Napht	21600	3.17	23500	25000	4.22
1-Napht-N=N-2-Napht	22000	3.18	25000	26300	4.29
2-Napht-N=N-2-Napht	22500	3.18	25500	25500 [a]	4.15 [a]

[a] Shoulders in the ascent side of the second $\pi \rightarrow \pi^*$ band.

3.2. Intensity of the $n \rightarrow \pi^*$ Band in the Absorption Spectrum

The intensities of the $n \rightarrow \pi^*$ bands of substituted azobenzenes are also only slightly affected by the nature of the substituent (Table 2); for the diarylazo compounds in Table 3, the intensity of the $n \rightarrow \pi^*$ band depends only on the nature of the substituent, and not on its position in the aromatic ring.

The intensity of the $n \rightarrow \pi^*$ band of *trans*-azobenzene decreases with falling temperature (Fig. 2).

The intensities are generally greater for the *cis* azo compounds than for the *trans* isomers (Tables 1, 2, and 4). The oscillator strength of *cis*-azobenzene is of an order of magnitude that is normally restricted to $\pi \rightarrow \pi^*$ transitions.

3.3. Vibrational Structure of the Electronic Bands

3.3.1. Vibrational Structure of the $n \rightarrow \pi^*$ Band

Vibrational structures of electronic bands are normally most pronounced in gas spectra, and the $n \rightarrow \pi^*$ bands usually have a more sharply defined structure than the $\pi \rightarrow \pi^*$ bands[28]. However, the $n \rightarrow \pi^*$ band of gaseous azobenzene[29], and also the long-wave bands of the azoalkanes, are without structure[17,30]; on the other hand, the structures of the $n \rightarrow \pi^*$ band are extremely sharp in *(3)* and *(4)*[20] (Fig. 3a).

Structured $n \rightarrow \pi^*$ bands have not been found in solution for *trans*-azobenzene or *cis*-azobenzene. Even low-temperature spectra (Figs. 2 and 4) and the spectrum of a solution in polyethylene show only continuous $n \rightarrow \pi^*$ bands[29]. Attempts to influence the shape of the $n \rightarrow \pi^*$ band by fixation of the molecule on surfaces have also been unsuccessful[31].

The solution spectra of the acyclic *trans* azo and *cis* azo aliphatic compounds (Table 1) also contain only unstructured bands (Fig. 3b)[16,17]. In contrast, the cyclic aliphatic azo compounds *(3)* and *(4)* in apolar solvents exhibit very sharp structures (Fig. 3b)[20,32]. Distinct structures are observed in the low-temperature spectra of the pyrazolines *(5)* and *(7)*, whereas *(6)* gives a smooth $n \rightarrow \pi^*$ band even under these conditions (Fig. 5)[18].

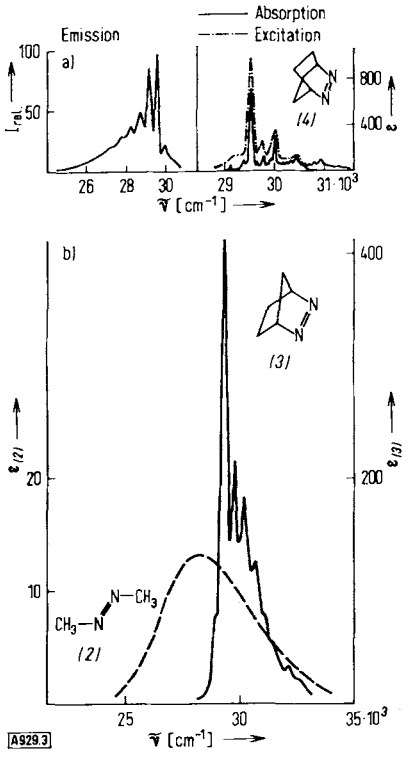


Fig. 3. a) Gas spectra of *(4)* [20]; b) absorption of ——— *(3)* in isooctane [32], --- *trans-(2)* in hexane.

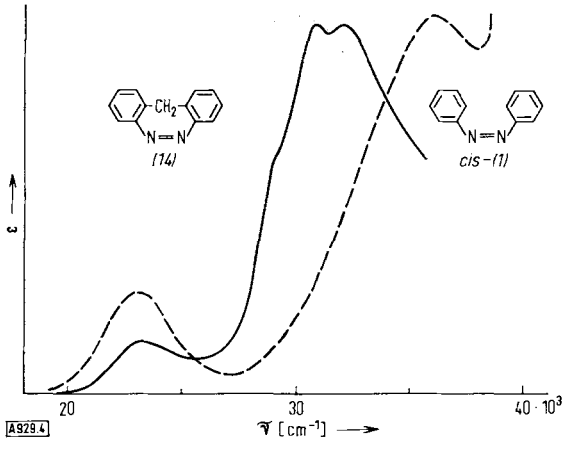


Fig. 4. Absorption of *cis*-azobenzene - - - - - and *o,o'*-azodiphenylmethane ——— in methylcyclohexane/isopentane at 77 °C.

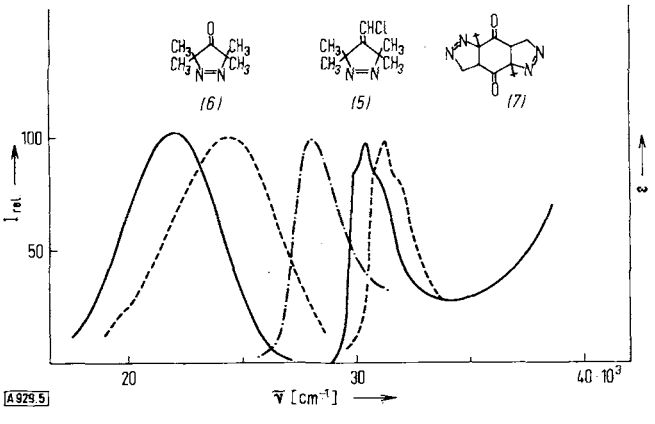


Fig. 5. Absorption and fluorescence of *(7)* - - - - - and *(5)* ——— and absorption of *(6)* -·-·-.

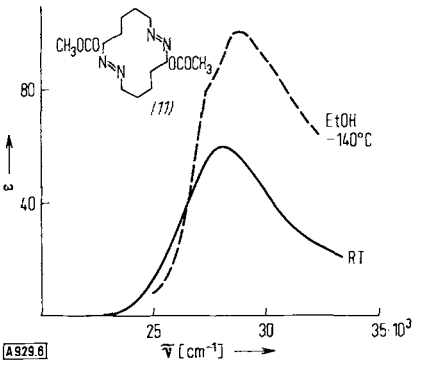


Fig. 6. Absorption of *(11)*.

The *o*-diazines *(8)*, *(9)*, and *(10)* give distinctly structured n→π* bands in apolar solvents, even at room temperature[33-35].

Owing to its solubility properties, a low-temperature spectrum can be recorded for the cyclic *trans* azo compound *(11)* only in polar solvents. In ethanol and ether-ethanol-ethyl acetate mixtures, a shoulder (Fig. 6)[36] appears on the n→π* band at low temperatures.

The crystal spectrum of azobenzene (transmission at 298 and 77 °K and reflection at room temperature) shows only a continuous n→π band[29]. A hint of a structure was found in the low-temperature spectrum of azobenzene in a stilbene host crystal at 77 °K[37], while the n→π* band in the spectrum of azobenzene in a bibenzyl crystal at 20 °K is unstructured[38].

3.3.2. Vibrational Structure of the Low-Energy π→π* Band

The π→π* bands behave quite differently from the n→π* bands with regard to their vibrational structure. The gas spectrum of azobenzene contains a sequence of vibrational bands separated by intervals of 220 cm^{-1}[39,40] and of 1300—1400 cm^{-1}[29].

The π→π* band of *trans*-azobenzene shows a hint of structure in apolar solvents, and this structure becomes sharp for solutions in polyethylene or in solid glasses at 77 °K (Fig. 2)[29].

The π→π* band of *cis*-azobenzene shows no structure even at 77 °K[20], whereas the bridged *o,o'*-azodiphenylmethane *(14)*, in addition to a large red shift and an increase in intensity, gives a structured π→π* band with intervals of 1400—1600 cm^{-1} between the maxima (Fig. 4, Table 4)[19].

The π→π* bands of *o*-diazines are strongly structured; the aromatic character of these compounds is dominant in this respect.

3.4. Emission of Azo Compounds

3.4.1. *trans* Azo Compounds

At present hardly any[*] acyclic *trans* azo compounds are known that exhibit emission, even under conditions that normally promote such behavior, such as deuteration,

[*] Some exceptions are being investigated at present. The reason for the emission of these compounds seems to be the exchange of the $^1(n,\pi^*)$- and $^1(\pi,\pi^*)$-states on the energy scale [31, 41].

incorporation in a vitreous matrix, incorporation in a solid solution, low temperatures, *etc.*

The cyclic *trans* azo compound *(11)* does not fluoresce, even at low temperatures[36], either in solution or in the crystalline state where the azo groups are planar[42]. In ethanolic solution *(12)* fluorescences weakly at room temperature and fairly strongly at low temperatures. Closer investigations lead, however, to the conclusion that it is not the azo form of the molecule that is the emitting species but probably some other tautomeric form[36].

3.4.2. *cis* Azo Compounds

The acyclic aliphatic or aromatic azo compounds in the *cis* configuration do not emit, nor do the nonplanar molecules *o,o'*-azodiphenylmethane *(14)* and *o,o'*-azobibenzyl[19], which are related to *cis*-azobenzene.

Among the cycloaliphatic compounds in Table 1, the rigid bicyclic molecules have higher fluorescence quantum yields than the planar pyrazolines. Diazacyclohexene *(13)* does not fluoresce.

3.4.3. *o*-Diazines

Emission is the rule rather than the exception for these compounds. Pyridazine *(8)*[33] and benzo[*c*]cinnoline *(10)*[35] fluoresce, and phthalazine *(9)*[43,44] phosphoresces.

3.4.4. Protonated Azo Compounds

Azo compounds dissolve readily in strong acids with asymmetric protonation[45,46] and concomitant disappearance of the n→π* band in the absorption spectrum. Almost without exception, the protonated azo compounds fluoresce[47]. Without the low-lying ^{1}(n,π*) state, however, the protonated molecules are spectroscopically no longer azo compounds.

3.4.5. Hydroxy Azo Compounds

Another class of azo compounds that can fluoresce embraces the *o*- and *p*-hydroxy derivatives. However, this fluorescence is due to the tautomeric hydrazone form[48,49].

3.5. Position of the Triplet States in Azo Compounds

Triplet states have not so far been observed for any normal azo compound by the usual spectroscopic methods.

For pyridazine[50] and benzo[*c*]cinnoline[51] it was possible to identify the lowest triplet states, from the crystal absorption spectrum at 4.2 °K, as the ^{3}(n,π*) and the ^{3}(π,π*) states, respectively; phthalazine phosphoresces[44].

In addition to spectroscopic measurements, photosensitized reactions can also provide information about the position of the triplet levels. Azobenzene can undergo photosensitized isomerization, thus revealing that the triplet state lies below 21000 m^{-1}[52]. Azoalkanes quench the phosphorescence of acetone and biacetyl[53]; the singlet-triplet difference is 3000 to 4000 cm^{-1}. A similar split of about 2500 cm^{-1} is found for *(3)*[54]. These results are of the expected order of magnitude[30].

4. Electronic States of the Azo Compounds

4.1. (π,π*) States

The bands of the azo compounds that are attributable to π→π* transitions are very similar to those of the analogous hydrocarbons. Useful methods based on molecular orbital (MO) theory are available for calculation of the π orbitals and π→π* transitions.

One approach using the MO model proceeds according to the "molecules in molecule" (MIM) concept starting from the assumption that the azo compounds consist of more or less strongly coupled electronic subunits; azobenzene, for example, is regarded as two benzene systems and the azo group[55]. This approach is favored by the molecular geometry (Section 2.2). It can be seen from Figure 7 that there is only a small difference between the MO and the MIM energy level diagrams in the simple Hückel-MO approximation.

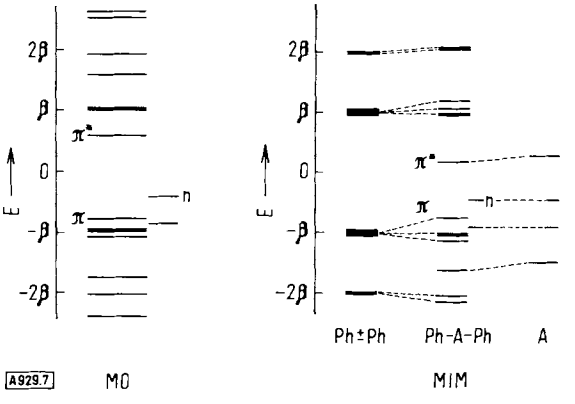


Fig. 7. Energy level diagram of azobenzene in the Hückel MO and MIM approximations.

cis Azo compounds are mostly nonplanar. When this is taken into account, it is possible to simulate the observed solution spectra[25,56]. The effect of steric factors[54,57-59] on the π→π* bands is clear from Figure 4.

4.2. (n,π*) States

4.2.1. MO Model

The n orbitals of the azo group have a symmetry property of the σ-bond skeleton: unlike the π orbitals, they are symmetrical on reflection in the plane of the molecule. If two n orbitals are situated close enough together, as in the azo group, MO theory predicts that they can combine in the same way as the p_z orbitals of the C atoms in conjugated molecules. The two n orbitals then split up into a group orbital having a higher energy and one having a lower energy (Figs. 1d and 8). The functions of the new states, which have definite symmetry properties that differ in the *trans* and in the *cis* isomers, can be expressed in this method as a linear combination of the original n orbitals. Since the group orbitals n_a and n_s are both doubly occupied, they contribute practically nothing to the bond energy.

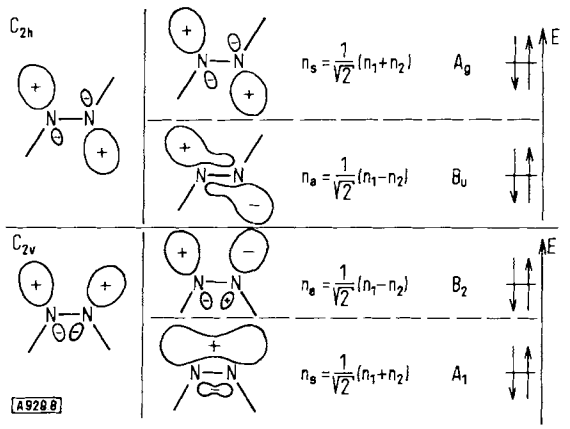


Fig. 8. The n orbitals of the *trans* and *cis* azo compounds in the MO model.

The magnitude of the n_a—n_s splitting has been the subject of a series of theoretical studies within the MO concept. Small values[60] and values of the order of 10000 cm^{-1}[25,37,61] have been calculated for aromatic azo compounds and *o*-diazines. An *ab-initio* calculation even gives 30000 cm^{-1} for diimine HN=NH[30].

In the MO model, the selection rules for *trans* and for *cis* azo compounds are different. For *trans*-azobenzene, the low-energy n→π* band belongs to a forbidden transition, whereas the transition to the higher $^1(n_a,\pi^*)$ state, with the polarization direction perpendicular to the plane of the molecule, is allowed. The situation is reversed for *cis*-azobenzene; the transition to the lowest $^1(n_a,\pi^*)$ state is allowed, again with the polarization direction perpendicular to the plane of the molecule.

In the MIM modification the n_a—n_s splitting is retained on symmetry grounds.

4.2.2. Exciton Model

When an electron localized in an n orbital of a hetero atom is excited into a π* orbital, a positive hole remains behind on the hetero atom, and this must influence the negative charge in the delocalized π* orbital. The charge distributions in the (n,π*) and (π,π*) states will therefore be fundamentally different. If the attraction between the electron and the hole is very strong, the (n,π*) state may be described essentially by an electron-hole pair, *i.e.* an exciton[62].

In molecules such as the *o*-diazines and the azo compounds, two such exciton centers are sufficiently close together for the interaction of the equally large transition moments M_a and M_b to lead to splitting of the exciton states[62,63]. Even when M is small, the splitting can be considerable in azo compounds and *o*-diazines because of the short distance d_{ab} between the centers in a molecule, according to[64]

$$\Delta E = \frac{2M_aM_b}{d_{ab}}.$$

In the exciton model, the selection rules for *cis* and *trans* azo compounds are the same. The position of the transition moments leads to the selection rules for "card-packed dimers"; the low-energy exciton transition is always forbidden, and the other transition is allowed[62–64].

A first theoretical approach has been made to find a model for the n→π* excitation that attempts to combine the elements of the MO and exciton models[65]. However, it has not yet been adapted for azo compounds.

4.2.3. *Ab-Initio* Calculations

The semiempirical MO and exciton models start with the assumption that the n orbitals are localized on the nitrogen atoms. This basis appears uncertain from *ab-initio* calculations. Calculations by various methods for pyrazine lead to the conclusion that the highest occupied n orbital of the ground state has a large share in σ orbitals of other atoms[66,67]. A geometry-dependent participation of the s electrons of the hydrogen in the n orbitals of the azo group is also found from calculations on diimine[30].

This result throws much greater doubt on the applicability of the exciton model than on that of the MO model, since the symmetry properties of the group orbitals at least are retained in the latter case.

4.2.4. Comparison of the Models with Experiment

The correct model must first reproduce correctly the following properties of the spectra of azo compounds: similar energy of the $^1(n,\pi^*)$ states in most of the azo compounds (Tables 1—3), splitting of the n orbitals, and the selection rules.

A constant position of the n→π* bands in the spectrum is compatible with the exciton and the MIM models. The exciton transitions are localized on the nitrogen atom, and they are little influenced by the groups at either end of the azo moiety. A critical comparison of exciton and MO calculations favors the MO theory, since this agrees better with the experimental results[68].

In the MIM modification of the MO model, the π* orbital is a perturbed orbital of the azo group (Fig. 7). On substitution in the aromatic subsystem, therefore, the lowest unoccupied π* orbital is displaced relatively little, whereas the highest occupied π orbital, an orbital of the aromatic subunits, is sensitive to substituents. Thus the π→π* band is displaced on substitution in the phenyl groups of azobenzene or on replacing the benzene by naphthalene moieties, whereas the n→π* band is not. The n→π* transition is localized in the azo group, *i.e.* it is not a charge transfer transition. However, the n→π* band is displaced if the substituent on the phenyl group also carries azo groups, as in bisazobenzene, trisazobenzene, tetrakisazobenzene, *etc.*, since the n orbitals of the individual azo groups can then interact with one another.

The strange similarity of the intensities (Table 3) of the n→π* bands of *trans*-1,1'- and -2,2'-azonaphthalene (symmetry C_{2h}) and *trans*-1,2'-azonaphthalene (symmetry C_s) can also be reconciled with the MIM model. The intensity of the n→π* band is determined only by the nature of the residues on the azo group, and not by the total symmetry of the molecule, as long as the configuration of the azo group itself is not altered. If the configuration is altered, the probability of transition is greatly increased in the *cis* isomer (Table 1). These selection rules provide the strongest argument in favor of the MO model.

Experimental checking of the splitting of the n orbitals as required by the models is hindered by the fact that only the one low energy n→π* band can be satisfactorily assigned in the azo compounds. Numerous attempts have been made to identify weak bands in the spectra of aromatic and aliphatic azo compounds as the second n→π* transition[16,69,70], but these assignments can hardly be regarded as final. However, the splitting of the n orbitals of the ground state is clearly recognizable in the photoelectron spectrum[71], where it has a magnitude of 26000 cm^{-1}

On the other hand, measurements on diazines point to several weak transitions in the region of the long-wave n→π* band[62,72,73]. However, the results are partly contradictory, and the identification of these transitions has not been verified[94].

4.3. Interactions of the Lowest $^1(n,\pi^*)$ State with Other Molecular States

4.3.1. Vibrational Coupling with the Lowest $^1(\pi,\pi^*)$ State

According to the MO theory, which we now favor, the n→π* transition is forbidden in the *trans* azo compounds. The observed intensity is nevertheless unusually high, and for *trans*-azobenzene it is actually higher than for the closely related benzo[*c*]cinnoline, for which the transition is allowed. The reason for this must be that the $^1(n,\pi^*)$ state is not pure (Section 2.1) but is coupled with other states. Such coupling is possible, *e. g.* through a deformation of the molecular field of a certain symmetry by corresponding vibrations or deviations from the planar arrangement of the atoms.

The transition moment $M_{00}^{i\mu}$, which corresponds to the intensity of the transition from the vibrationless electronic ground state $(\theta_0^{(0)}\cdot\varphi_0^0)$ to the μ-th vibrational state of the electronically excited state *i* $(\theta_i^{(0)}\cdot\varphi_\mu^i)$, is

$$M_{00}^{i\mu} = e\int\theta_0^{(0)} r \theta_i^{(0)} d\tau \times \int\varphi_0^0\varphi_\mu^i dq = m_0^i \langle\varphi_0^0|\varphi_\mu^i\rangle \qquad (3)$$

and taking into account the vibrational coupling[74]:

$$M_{00}^{i\mu} = m_0^i \langle\varphi_0^0|\varphi_\mu^i\rangle + \sum_{j\neq i} m_0^j \frac{\int\theta_i^{(0)}\mathbf{V}_\mu\theta_j^{(0)}}{E_j^{(0)} - E_i^{(0)}} d\tau \times \int\varphi_0^0 q_\mu \varphi_\mu^i dq \qquad (4)$$

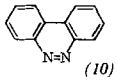
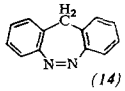
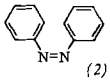
$\mathbf{V}_\mu$ is the operator of the perturbation of the nuclear field by the vibration μ, q_μ is its normal coordinate, and $E_i^{(0)}$ is the position of the pure electronic level *i* in the energy level diagram. If the transition to the state is electronically forbidden, $m_0^i = 0$, and the observed intensity must be "stolen" from states *j* whose m_0^j is large.

The integrals conceal the selection rules, which can be determined by the use of the character tables; the transition is allowed only if the sign and magnitude of the integrand are unchanged by any symmetry operations that are possible for the molecule in question.

For the *trans* azo compounds, coupling between the $^1(n,\pi^*)$ state and the neighboring allowed $^1(\pi,\pi^*)$ state is possible through an out-of-plane deformation vibration. This brings the polarization direction of the n→π* transition into the direction of the transition moment $m_0^{(\pi,\pi^*)}$. Both bands of *trans*-azobenzene are in fact polarized in the plane of the molecule[17,29,37]. This rules out any possibility that this n→π* transition is allowed, and hence also rules out the applicability of the exciton theory.

An interaction of this type must influence both of the coupled states. This can be seen directly on comparison of the vibrational bands of the π→π transition in the low-temperature spectrum of stilbene and of azobenzene in the bibenzyl host lattice. The bands are about 15 times as broad in the case of azobenzene[38]. The effect of coupling can also be demonstrated by the influence of increasing deviations from a planar molecular structure on the allowed n→π* transition of the *cis* azo compounds. Table 4 shows the correlations between molecular geometry and vibrational structure, intensity of the n→π* band, and fluorescence yield.

Table 4. Correlation between molecular geometry and spectroscopic properties of *cis* azo compounds.

Molecule	n→π*-band structure	ε_{max}	π→π*-band structure	ε_{max}	Fluorescence yield [%]
 *(10)*	pronounced 350 500 cm^{-1}		sharp 500, 1250 cm^{-1}	1500	0.7
 *(14)*	none	970	RT: none 77 °K: weak 1400 cm^{-1}	9900	—
 *(2)*	none	1470	none	5200	—

Benzo[*c*]cinnoline is actually an azo compound rather than a diaza-aromatic compound. The absorption and emission properties[75] can be satisfactorily described by the MIM model.

4.3.2. Interaction with Other States

There is no doubt that the intensity of the n→π* band in the *trans* azo compounds is "stolen" from the π→π* transition. However, this does not necessarily lead to loss of the vibrational structure, as is shown by the sharply structured benzene band at 40000 cm^{-1}.

The overlap integral of the vibrational functions, the so-called Franck-Condon (FC) factors in equation (3), differs from zero only for vibrations of the same symmetry. It is therefore expected that only totally symmetrical vibrations μ determine the structure of the electronic bands. This is observed for the benzene band, and for *trans*-azobenzene one also finds the totally symmetrical N—N stretching vibration at 1400 cm^{-1} in the π→π* band and the totally symmetrical in-plane deformation vibration at 220 cm^{-1}[76]. The n→π* band, however, is structureless.

A band form of this type may be due to a quasi-continuum or to a true level broadening.

A quasi-continuum is observed when the distance between discrete bands is smaller than their half-width. This is possible *e. g.* for polyatomic molecules of low symmetry, where very many vibrations may be stimulated with the

electronic transition. The molecules of azobenzene or azomethane on the other hand, are too small and their symmetry too high for this to occur.

True level broadening is to be expected if, according to the Heisenberg uncertainty relation

$$\Delta t \times \Delta E = 5.25 \times 10^{-12}\ [\mathrm{cm}^{-1}\,\mathrm{s}]$$

the true lifetime $\tau = \Delta t$ of an excited vibronic state is sufficiently small. Line widths of 220 and 1500 cm^{-1} correspond to lifetimes of 2.5×10^{-14} and 3×10^{-15} s respectively.

The intrinsic lifetime of a state, τ_0, which is determined by the rate of the resonance fluorescence, can be calculated from the intensity of the corresponding absorption band[77], and is $\tau_0 = 5 \times 10^{-7}$ s for the $^1(n,\pi^*)$ state of *trans*-azobenzene. This lifetime may be shortened by radiationless processes, which are faster than the emission of light. However, a radiationless transition between two states is possible only if the states are coupled.

The degree to which the states retain their individuality and can be identified in the spectrum is dependent upon the strength of coupling. If the energy of a system capable of vibrating is removed by very tight coupling before the characteristic vibrational motion can develop, the actual lifetime drops to below one vibrational period, and the individuality of this vibration is no longer recognizable. In molecular systems this means that the BO approximation is no longer valid. One interpretation of the lack of structure of the n→π* band of azo compounds would be the assumption of particularly tight coupling of the vibrations in the $^1(n,\pi^*)$ state. However, this is opposed by theoretical considerations[73] and the spectroscopic findings.

The fact that azo compounds do not fluoresce indicates that the coupling of electronic states is responsible for the shape of the n→π* band of the azo compounds. The processes that are important to the deactivation of an excited molecule are outlined in Figure 9.

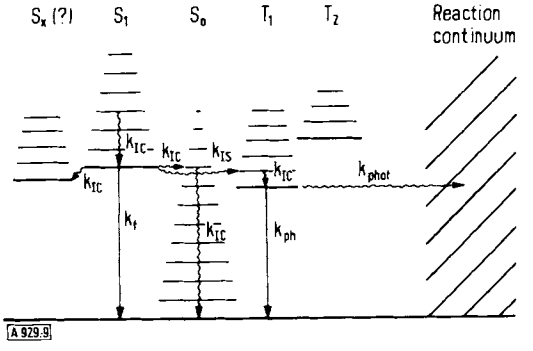


Fig. 9. Deactivation processes.

Transitions in the energy level system can be characterized by first order rate constants; k_f and k_{ph} are the constants for fluorescence and for phosphorescence respectively, k_{IC} is the constant for vibrational relaxation within a multiplicity, and k_{IS} and k_{phot} are the constants for the multiplicity change and for photochemistry.

The most extensively used model of radiationless deactivation[78–81] is based on coupling of the lattice vibrations of the solvent ψ_f, whose number is very large, with the vibrationless excited electronic state ψ', which is assumed to lose its energy non-radiatively (Fig. 10).

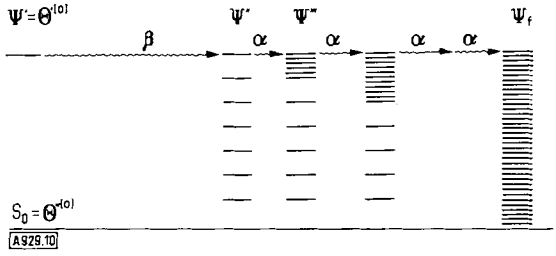


Fig. 10. Coupling in radiationless deactivation.

If only the initial state $\psi' = \theta_1 \cdot \varphi_0^1$ and the final state $\psi'' = \theta_0 \cdot \varphi_\mu^0$ (Fig. 10), a highly excited vibrational state of the electronic ground state, were coupled by a low interaction energy β, the molecular system would oscillate between the two states with a frequency of

$$\frac{1}{\tau} \approx \frac{\beta}{\hbar} = \frac{1}{\hbar} \int \theta_1 \mathbf{H}' \theta_0 \mathrm{d}\tau \, \langle \varphi_0^1 | \varphi_\mu^0 \rangle \qquad (5a)$$

where $\mathbf{H}'$ is the coupling operator. However, the final state is in interaction α with the environment, *i.e.* with the thermal vibrations of the solvent. According to spectroscopic findings, α is much greater than β, and the states ψ'', ψ''' *etc.* coupled with the final state are very numerous. The energy is very rapidly partitioned from the "hot" final state ψ'' over so many low excited vibrations of the solvent that the chance of an accumulation of energy to regenerate the final state ψ'' and reversion to the initial state ψ' is extremely small ($\tau_p = \infty$).

The BO approximation is assumed to be valid in Figure 10. The greater the coupling β, the faster is the radiationless deactivation. This is true even when the vibronic states ψ' and ψ'' have largely lost their identity, and one can therefore hardly expect a vibrational structure in the n→π* band.

There must thus be at least one vibronic state in the azo compounds at approximately the same energy as the $^1(n,\pi^*)$ state, with which the $^1(n,\pi^*)$ state can interact.

The first possibility would be a highly excited vibrational state of the ground state, as shown in Figure 10. However, the values of the FC factors, which can lie between 1 and 10^{-20} in the various cases[79], decrease roughly exponentially with the difference in the vibrational quantum numbers in the initial and in the final state[76]. Owing to the large energy difference $\psi' - S_0$ (Fig. 10), the FC factors are very small. Deuteration of the molecule, which causes the FC factors to decrease further and thus normally increases the fluorescence quantum yield[63,82], has no influence on the band shape and fluorescence in the case of azobenzene. This points to a small difference between the coupling vibrationless electronic states[83].

Optimal coupling would be offered by a singlet state S_x (Fig. 9) in the vicinity of the $^1(n,\pi^*)$ state. There need not be any measurable absorption corresponding to this state. However, there is no evidence of such a state for azo compounds, though evidence is found in the low-temperature spectra of the *o*-diazines[62]. The existence and identity of such a singlet state has yet to be confirmed.

The spectroscopic behavior of the azo compounds could also be explained by tight coupling of the $^1(n,\pi^*)$ state with a triplet state T_1 (Fig. 9). The prohibition of intersystem crossing would have to be overcome in this case. The $^3(n,\pi^*)$ state is situated only slightly below the $^1(n,\pi^*)$ state, and this leads to favorable FC factors. The coupling between singlet and triplet states corresponds to the spin-orbit interaction of the electrons, and the coupling energy is

$$\beta = \int {}^3\theta_i \mathbf{H}_{s.o.} {}^1\theta_i d\tau \langle \varphi_b^i | \varphi_\mu^i \rangle \qquad (5b)$$

The spin-orbit coupling operator $\mathbf{H}_{s.o.}$ has the symmetry properties of a rotation[84]; there are consequently also symmetry-dependent selection rules for the radiationless S→T transitions. Coupling between similar states, *e.g.* $^1(n,\pi^*)$ and $^3(n,\pi^*)$ states, is forbidden in *cis* azo compounds, but allowed in the *trans* isomers[44]. On the other hand, transitions between singlet and triplet states of different kinds are allowed. However, this electronic selection rule is strictly valid only if the configuration of the molecule is planar. Structured n→π* absorption bands and n←π* fluorescence can therefore be expected only for planar *cis* compounds where deactivation *via* the $^3(n,\pi^*)$ state is prevented, and this is in agreement with the experimental findings. The more resistant the skeleton to out-of-plane deformation vibrations, the sharper is the structure and the higher the fluorescence yield (Tables 1 and 4).

However, the energy of the $^3(\pi,\pi^*)$ state can be lower than that of the $^1(n,\pi^*)$ state for aromatic compounds. The probability of fluorescence would then be small. It is in fact found that benzo[*c*]cinnoline, for which the lowest triplet state is regarded as a $^3(\pi,\pi^*)$ state on the basis of vibrational analysis[51], has a fluorescence quantum yield of only 0.7%[75,85].

A possible objection lies in the question whether the mixing of states having different multiplicities can be sufficiently strong. Coupling is usually determined experimentally from quantum yield measurements; no answer can be given for the azo compounds concerned, owing to the absence of emission. However, the spin-orbit coupling depends on the gradient of the nuclear field, and because of their s character, the n electrons are much more exposed to this field than π electrons[81]. This coupling is also favored by any deviations from planarity of the molecule. A pathway *via* the triplet system is accepted for the photoisomerization[52,53,86].

A final possibility is the coupling of the lowest excited state with a dissociative molecular state. This is undoubtedly an important case for the aliphatic azo compounds. Both the vibrational structure and the fluorescence are more pronounced for the more photostable chloromethylenepyrazoline *(5)*[87] than for the more labile ketopyrazoline *(6)*. The weak shoulder observed for the n→π* absorption band of *(11)* could also be due to the very much higher photostability of this compound in relation to *trans*-azomethane[88].

The azobenzenes, and under certain conditions azoalkanes[82,86], are photostable apart from *cis-trans* isomerism. However, the molecule is not necessarily destroyed by a photoreaction. A transition of the excited molecule into a different form, *e.g.* a more extended form as an intermediate of the isomerization due to inversion at the nitrogen atom[89,90] before the totally symmetrical deformation vibration can become fully developed, may also be described by coupling of the $^1(n,\pi^*)$ state of the angular molecule with a state of the molecule having the transition geometry. The FC factors in equation (5) will become increasingly favorable with increasing difference in geometry between the coupling states.

The quantum yields of the isomerization of azobenzene are high[91], and the kinetic analysis calls for intermediate states[91,92]. The decrease in the quantum yield of the *trans-cis* isomerization[93] with falling temperature does not necessarily mean that the intermediate state is not reached, as long as the step that requires an activation energy takes place from this state.

Vibrational structure and fluorescence are therefore to be expected only for azo compounds that are stabilized in the *trans* or *cis* form. This is also largely in agreement with experimental results.

The last two possibilities are not mutually exclusive. The state that couples with the $^1(n,\pi^*)$ state is probably a triplet state with modified molecular symmetry. If the existence of such a state is accepted, the spectroscopic and photochemical results as a whole can be logically explained, particularly the kinetic analysis of the *cis-trans* isomerization[91] and the sensitization of this reaction[54,58].

5. Conclusion

The absorption spectrum of the azo compounds is best explained with the aid of an MO model in which the molecules are assumed to be built up from coupled electronic subunits. The electronic system of the azo group is significantly perturbed in the aromatic compounds, but the n→π* transitions are determined primarily by the local symmetry of the azo group, and not by the molecular geometry.

The $^1(n,\pi^*)$ states of the azo compounds exhibit unusual coupling properties. By vibrational coupling, the n→π* transition, which is forbidden for the *trans* isomers, "steals" its high intensity, which may exceed that of the corresponding allowed transition in a closely related *cis* molecule, from the neighboring allowed π→π* transition. The inability to fluoresce and the absence of a vibrational structure in the n→π* band for most azo compounds is due to the tight coupling of the $^1(n,\pi^*)$ state with a somewhat lower-lying molecular state, which is determined by symmetry-dependent selection rules for electronic states and by geometric factors. The identity of this state has not

yet been established; however, the experimental data point to a triplet state, probably with a molecular geometry that is strongly modified in relation to the configuration of the ground state.

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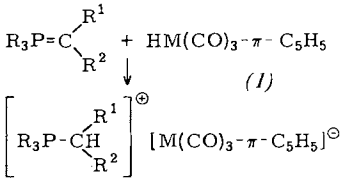
COMMUNICATIONS

Onium Salts Containing Carbonylmetalate Anions[1]

By *Wolfgang Malisch*[*]

Ylide chemistry has so far provided hardly any information regarding the reactivity of ylide systems toward transition metal complexes. While looking for metalate reagents suitable for the synthesis of metal-metalloid bonds, we have found that an acid-base reaction according to the following scheme occurs on treatment of carbonylmetal hydrides *(1)* with alkylidene or imino derivatives of phosphorus, arsenic or sulfur.

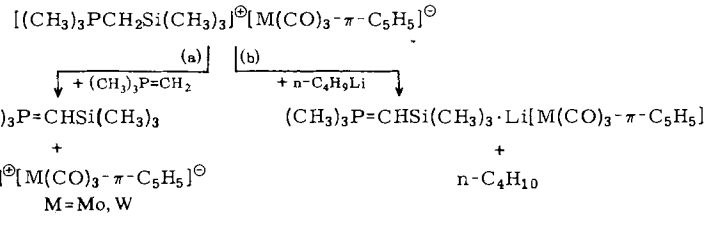


$R = CH_3, C_2H_5, C_6H_5$

$M = Cr, Mo, W$

With ylides of slight basicity, such as the compounds $(CH_3)_2S(O)CHSi(CH_3)_3$ or $(CH_3)_3PNSi(CH_3)_3$, the addition is followed by loss of the trimethylsilyl group, so that silyl-free onium salts result. The most strongly acidic representative of the carbonyl hydride derivatives of VIb transition metals, namely, $HCr(CO)_3$-π-C_5H_5, also undergoes desilylation even on reaction with the phosphorus-silyl ylides[2].

The structures of the products, which are pale yellow salts, sensitive to oxygen, can be proved by analysis and NMR and IR spectroscopy[5]. Their behavior towards organometallic bases in transylidation and deprotonation processes [(a) and (b), respectively] is comparable with that of onium halides[6].



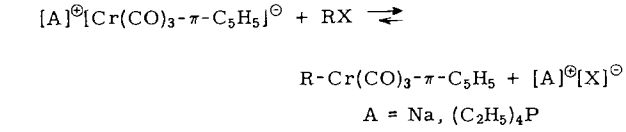
M = Mo, W

Of the onium salts studied so far, a few are extremely reactive. Their use for transfer of the complex metalate ion, with formation of metal-metalloid bonds[1,7] is particularly advantageous in apolar solvents, for with some cat-

Table 1. Properties of some onium carbonylmetalates [3].

Starting ylide	Cation	Products M in $[M(CO)_3$-π-$C_5H_5]^-$	M. p. (°C) [a]	ν_{CO} [b]
$(CH_3)_3P{=}CH_2$	$(CH_3)_4P$	Cr	246–248	1895, 1758
		Mo	246–249	1898, 1760
		W	266–269	1888, 1750
$(C_2H_5)_3P{=}CHCH_3$	$(C_2H_5)_4P$	Cr	94–98	1892, 1765
		Mo	115–117	1889, 1761
		W	107–109	1887, 1764
$(CH_3)_3P{=}CHSi(CH_3)_3$	$(CH_3)_3PCH_2Si(CH_3)_3$	Mo	98–101	1894, 1768
		W	107–109	1890, 1762
$(CH_3)_3P{=}C[Si(CH_3)_3]_2$	$(CH_3)_3PCH[Si(CH_3)_3]_2$	Mo	125–128	1893, 1763
		W	139–142	1887, 1759
$(CH_3)_2S(O){=}CH_2$	$(CH_3)_3S(O)$	Cr	131–133	1894, 1759
		Mo	116–119	1892, 1767
		W	120–122	1888, 1762
$(CH_3)_3P{=}NH$	$(CH_3)_3PNH_2$	Cr	173–176	1892, 1752
		Mo	125–128	1885, 1752
		W	<185	1893, 1755

[a] Closed capillary (N_2). All the compounds melt with decomposition.
[b] Measured as Nujol suspension.



A = Na, $(C_2H_5)_4P$

R	X	ν_{CO}	M.p. (°C)
$(CH_3)_3Si$	Br	1992, 1924, 1897	Dec. at room temp.
$Cl(CH_3)HSi$	Cl	2012, 1944, 1913	47–49
Cl_2HSi	Cl	2027, 1962, 1932	119–122

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ions the solubility suffices for reaction with halides of IV b elements and there is a minimum of reverse fission of the product[8]. The yields are then generally higher than when the analogous alkali-metal salts are used.

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[3] Peralkylated members can also be obtained by fission of the trimethylsilyl derivatives of the above mentioned metals by tetraorganofluorophosphoranes [4]: $(CH_3)_3SiM(CO)_3$-π-$C_5H_5 + R_4PF \rightarrow [R_4P][M(CO)_3$-π-$C_5H_5] + (CH_3)_3SiF$

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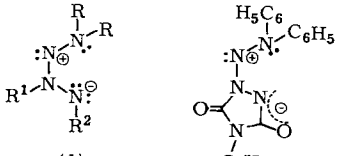
Structure of Aminoazimines

By *J. E. Weidenborner, Egon Fahr, Monika J. Richter*, and *K.-H. Koch*[*]

Addition of aminonitrenes to azo compounds yields aminoazimines *(1)*[1,2]. Conclusive proof of the structure[3] of this new class of compounds has now been provided by X-ray structure analysis of the aminoazimine *(2)*[4].



(1)

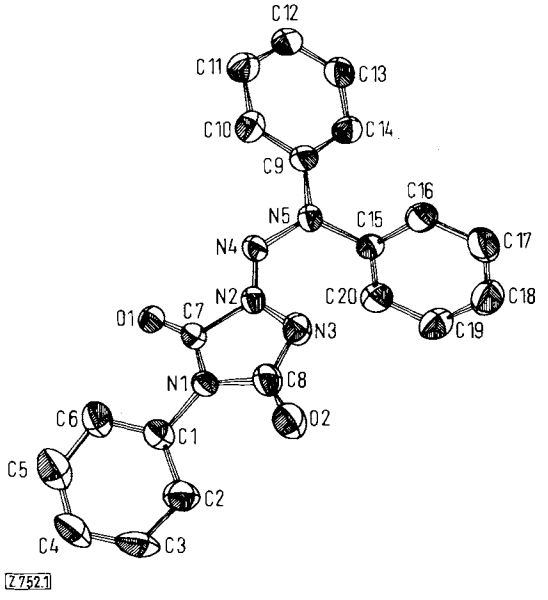
(2)

The compound crystallizes in the triclinic space group $P\bar{1}$ with $a = 12.503 \pm 0.004$, $b = 8.100 \pm 0.006$, $c = 9.610 \pm 0.003$ Å, $\alpha = 96.24 \pm 0.03°$, $\beta = 95.04 \pm 0.02°$, $\gamma = 115.63 \pm 0.03°$; d_{exp} (aqueous NaBr solution) $= 1.373$ g cm^{-3}, d_{calc} $(Z = 2) = 1.376$ g cm^{-3}.

Single crystal intensity data were measured on a CCXD four-circle computer-controlled X-ray diffractometer[5] and a total of 1717 non-zero independent reflections were recorded. The usual Lorentz-polarization corrections were applied and normalized structure factors (E-factors) were calculated using the scale factor and overall temperature factor obtained by *Wilson*'s method[6]. The structure was solved by the symbolic addition procedure[7], implemented with a version of the SORTE program[8,9] written for the IBM 360/91 computer. Three symbols were introduced and a total of 333 signs were generated for reflections with $E > 1.45$. The eight possible E-maps were synthesized and only one of these revealed clearly the positions of the 27 non-hydrogen atoms. This trial structure gave a value of

$$R = \frac{\Sigma ||F_o| - |F_c||}{\Sigma |F_o|} = 34\%.$$

Refinement was accomplished by the method of least squares. Hydrogen atoms were located on a difference Fourier map and their positions included in the refinement which was terminated at $R = 6.1\%$. The molecular structure is shown in Figure 1.



Z 7521

Fig. 1. Structure of 2-(diphenylaminoaminylio)-3,5-dioxo-4-phenyl-1,2,4-triazolidin-1-ide *(2)*. The interatomic distances and bond angles (estimated standard deviations in parentheses are in units of the last place) are as follows:

C 1—N 1 = 1.435(8) Å	N 4—N 5 = 1.340(7) Å
C 7—N 1 = 1.333(7) Å	C 9—N 5 = 1.429(8) Å
C 7—N 2 = 1.497(7) Å	C 15—N 5 = 1.447(8) Å
N 2—N 3 = 1.360(7) Å	C 7—N 1—C 8 = 110.2(9)°
C 8—N 3 = 1.344(8) Å	N 1—C 7—N 2 = 102.0(7)°
C 8—N 1 = 1.445(8) Å	C 7—N 2—N 3 = 112.3(8)°
C 7—O 1 = 1.197(7) Å	N 2—N 3—C 8 = 105.1(8)°
C 8—O 2 = 1.211(8) Å	N 3—C 8—N 1 = 110.3(8)°
N 2—N 4 = 1.269(7) Å	N 2—N 4—N 5 = 116.9(9)°

X-ray structure analysis demonstrates, surprisingly, that the molecule is separated into two isolated conjugated

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systems by the single bonds C7—N2 and C8—N1. The three nitrogen-nitrogen bonds are all shorter than the usual single N—N distance of 1.44 Å[10,11], and the N2—N4 distance is only slightly longer than the 1.24 Å expected for a double bond[10,11]. A calculation of the best least-squares plane passing through the atoms forming the five-membered ring was performed to determine its conformation, and can be represented by the equation

$$0.4001\,x + 0.7802\,y - 0.4808\,z = 1.918$$

The displacements of the five atoms from this plane (with standard deviations in parentheses) are small but significant

N1	0.017(5) Å
C7	−0.013(6) Å
N2	0.004(5) Å
N3	0.007(5) Å
C8	−0.015(6) Å

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The Wittig Reaction of Alkylidenetriphenylphosphoranes with Sodium α-Hydroxy Sulfonates

By *Gerhard Koszmehl* and *Bodo Bohn*[*]

In the Wittig olefin synthesis from alkylidenetriphenylphosphoranes and aldehydes[1] the aldehydes may be replaced by sodium α-hydroxy sulfonates (aldehyde hydrogen sulfite adducts) of the aliphatic, aromatic or heterocyclic series. Compared with the normal Wittig reaction, the new reaction, which is carried out under the same conditions, has the advantages of generally higher yields and purer products. The products are formed in one sterically favored form, if not actually stereospecifically, and are often precipitated immediately with the melting point of the pure *trans*- or all-*trans*-compound. The steric course of the reaction is strongly dependent on the solvent and on the nature and amount of the base used. Mechanistic studies are in progress.

$$(C_6H_5)_3\overset{\oplus}{P}\text{-}CH_2\text{-}R\ X^{\ominus} + R'\text{-}\underset{OH}{CH}\text{-}SO_3Na$$

$$\xrightarrow[-KX,\ -2\,C_4H_9OH]{+2\,KOC_4H_9} R\text{-}CH{=}CH\text{-}R' + (C_6H_5)_3PO + NaKSO_3$$

The best results with respect to steric course and yield are obtained by reaction for 1 to 2 hours at 60 °C in anhydrous DMF with addition of 2.2 mol of K *tert*-butoxide. The proportion of *trans*- or all-*trans*-compound is determined, not only by comparison of melting points, but also by IR and NMR spectroscopy as well as gas chromatography.

In some cases a sterically more favorable or stereoselective course of the normal Wittig reaction can be achieved by adding $NaHSO_3$. Such a sterically more favorable reaction is also possible up to a certain extent by addition of Li salts[2,3].

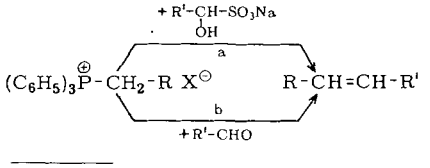
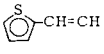
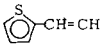


Table 1 shows that treating alkyltriphenylphosphonium salts with sodium α-hydroxy sulfonates gives higher crude yields and higher melting points of the crude products than are obtained from the aldehydes.

Table 1. Reactions of alkylidenetriphenylphosphoranes with a) sodium α-hydroxy sulfonates and b) aldehydes. Conditions: 1—2 hours at 60 °C in DMF under N_2.

R	X	R'	Route	Crude yield [%]	Crude m. p. [°C]	M. p. [°C] [a]
C_6H_5	Cl	C_6H_5	a	91	125	124–125
C_6H_5	Cl	C_6H_5	b	45 50	122 oily-solid	124–125
H_3C—C_6H_4	Br	H_3C—C_6H_4	a	89	180	177–178[4]
H_3C—C_6H_4	Br	H_3C—C_6H_4	b	79	150–170	177–178[4]
H_3CO—C_6H_4	Cl	O_2N—C_6H_4	a	82	128–130	129–130[5]
H_3CO—C_6H_4	Cl	O_2N—C_6H_4	b	43	105–125	129–130[5]
H_3CO—C_6H_4	Cl	O_2N—C_6H_4[b]	b	85	132–134	129–130[5]
C_6H_5	Cl	C_6H_4—CH=CH	a	60	148	152–153[6]
C_6H_5	Cl	C_6H_4—CH=CH	b	53	145–146	152–153[6]
	Cl		a[c]	81	173–174	170–171[7]
	Cl		b[d]	53	165–167 85–110	170–171[7]

[a] M.p. of the pure *trans*- or all-*trans*-compound.
[b] With addition of 1 and 2 equivalents of $NaHSO_3$ respectively.
[c] This compound was prepared also from triphenylthenylphosphonium chloride and NaO_3S—CH(OH)—CH(OH)—SO_3Na. Crude product: yield 85%; m.p. 171—172 °C.
[d] This compound was also prepared from triphenylthenylphosphonium chloride and $(OHC{-}CHO)_3 \cdot 2H_2O$. Crude product: yield 73%; m.p. 154—165 °C.

Olefins are also formed when alkyloxodiphenylphosphoranes, alkylphosphonates or alkylphosphinates are treated with sodium α-hydroxy sulfonates.

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[3] *M. Schlosser*, *K. F. Christmann*, and *A. Piskala*, Chem. Ber. *103*, 2814 (1970).
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5-Amino-1,2,4-thiadiazoles from 1-Amino-3-iminoisoindolenines

By *Klaus Leverenz*[*]

Dedicated to Professor Otto Bayer on the occasion of his 70th birthday

1-Amino-3-iminoisoindoleninium thiocyanates *(3)*, which can be prepared from the dinitriles *(1)* by way of 1-imino-3-

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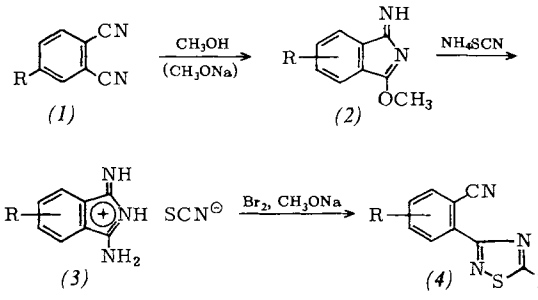
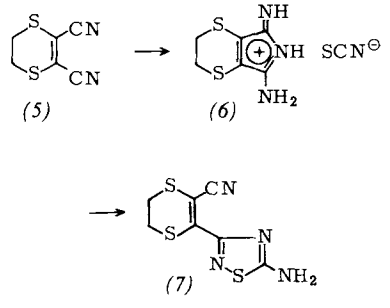
methoxyisoindolenines *(2)*[1], can be converted into 5-amino-1,2,4-thiadiazoles *(4)* by simultaneous action of bromine and sodium methoxide. It was not possible to separate the thiadiazoles *(4)* with $R = OCH_3$ or C_6H_5 into isomers even by thin-layer chromatography.



	R	M.p. (°C)
(4a)	H	240
(4b)	OCH_3	236—238
(4c)	C_6H_5	225—228

The thiadiazole *(7)*, m.p. 223—224 °C, is formed by a similar reaction sequence from the dinitrile *(5)* by way of the thiocyanate *(6)*.



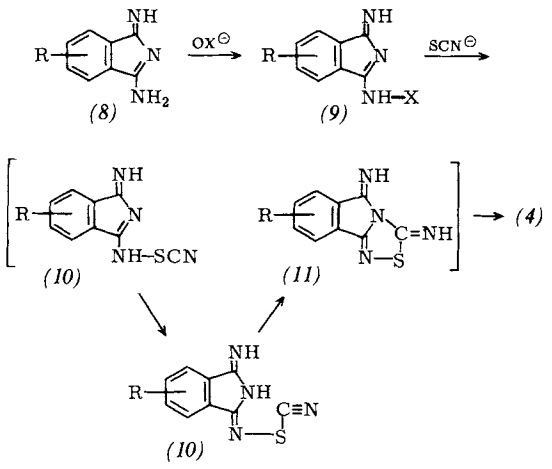
The thiocyanates *(3)* and *(6)* thus behave like open-chain amidinium thiocyanates in the thiadiazole synthesis discovered by *Goerdeler*[2]. It appears that the present reaction probably also proceeds *via* the *N*-bromo compound.

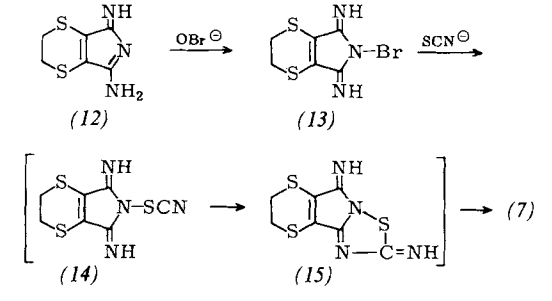
Experimentally, the 1-amino-3-iminoisoindolenines *(8)* and *(12)* can be converted by hypohalites into *N*-halo derivatives of the probable constitutions *(9)* and *(13)*, respectively, which react with alkali-metal or alkaline-earth thiocyanates in alcohols, dimethylformamide, or pyridine even at room temperature.

Since the 1-amino-3-iminoisoindolenines *(8)* and *(12)* are produced on a technical scale ("phthalogenes") and the above reactions can be conducted without intermediate isolation this reaction sequence provides a simple synthesis of the new 5-amino-1,2,4-thiadiazoles which in turn can find application in the production of azo dyestuffs[3].

General procedure:

1-Amino-3-iminoisoindolenine (1 mol) is added with stirring to a solution of KOH (1.15 mol) in methanol (1 liter) at 0—5 °C. Bromine (1 mol) is then added dropwise over *ca.* 2 h at −5 to −2 °C; this should not cause the pH to fall below 7, and, if it does, methanolic KOH should be added. The mixture is stirred for a further 2 h at *ca.* 0 °C, after which KSCN (1 mol) is introduced portionwise over *ca.* 15 min, starting at *ca.* 10 °C and without further





R = H, OCH_3, C_6H_5; X = Cl, Br

	R	X	M.p. (°C)
(9a)	H	Cl	310—315 (dec.)
(9b)	H	Br	331—334
(9c)	OCH_3	Cl	250 (dec.)
(9d)	OCH_3	Br	250—251
(9e)	C_6H_5	Br	209—211
(13)	—	Br	166—167 (dec.)

cooling. The temperature rises to 35—40 °C. To complete the reaction, the mixture is warmed for 2 h at 45—50 °C, after which the *N*-bromo compound should be no longer detectable by KI-starch paper. After a further 12 h at 20 °C the precipitate is collected and washed with methanol and finally with water until salt-free. The yields amount to 60—85%. For further purification, the 5-aminothiadiazoles can be reprecipitated from pyridine/water (2:1).

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[2] *J. Goerdeler*, Chem. Ber. *87*, 57 (1954).

[3] *K. Leverenz*, DOS 2106585 (1971), Bayer AG.

Nitrile/Amine Conproportionation to Two Imines[**]

By *Hans-Dieter Scharf* and *Ludwig Kamm*[*]

On refluxing the violet azo dye 2-[*p*-(diethylamino)-phenylazo]-5-nitrobenzonitrile *(1)*[1] with *n*-butylamine *(2a)*, cyclohexylamine *(2b)*, or benzylamine *(2c)* we

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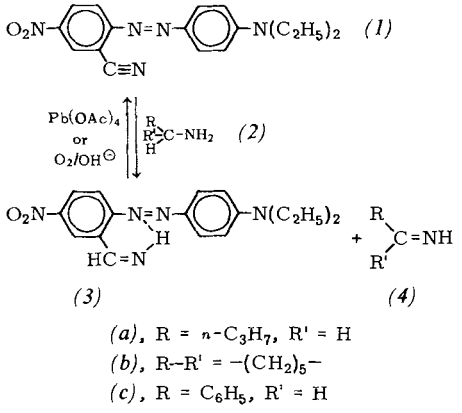
observed a surprising reaction involving uncatalyzed hydrogen transfer from these amines containing α-hydrogen atoms to the aromatic nitrile group with formation of two imine groups. Besides *(1)*, it is so far known that 5-nitroanthranilonitrile (2-amino-5-nitrobenzonitrile) and its *N,N*-dibenzoyl derivative undergo this reaction.



(a), R = n-C_3H_7, R' = H
(b), R–R' = $-(CH_2)_5-$
(c), R = C_6H_5, R' = H

Good yields of the orange-red imino dye *(3)* and the imines *(4a)*, *(4b)*, and *(4c)* are formed respectively, the latter being identified as 2,4-dinitrophenylhydrazones after hydrolysis.

The structure of *(3)* was proved by IR (KBr) and mass spectroscopy[2] as well as by Stephen reduction[3] of *(1)*. Hydrolysis of the resulting immonium hexachlorostannate affords the imine *(3)*. The CN stretching vibration at 2230 cm^{-1} for *(1)* is absent for *(3)*. In its place, three bands appear in the region of N—H stretching frequencies at 3450, 3300 and 3130 cm^{-1} that are to be ascribed to the influence of hydrogen bonding[4]. The IR spectrum (KBr) of *(3)* exhibits the C=N stretching vibration at 1630 cm^{-1} in front of the aromatic bands at 1600 cm^{-1} [in *(1)* and *(3)*][5]. The position of this C=N band is typical of aldimines containing NO_2-substituted phenyl rings[6, 7] and indicates an intramolecular hydrogen bond[8].

The mass spectrum of *(3)* contains, besides the molecular ion $M^+ = 325$, very intense peaks *m/e* 149^+ ($C_7H_5N_2O_2$) and 148^+ ($C_6H_{14}N$) corresponding to the two half-molecules left on removal of N_2. In addition, 149^+ undergoes further loss of 28 mass units (HC=NH). Thus all the relevant structural elements have been recognized.

The dyestuff imine *(3)* extremely difficultly hydrolyzable and reacts with $Pb(OAc)_4$[9] or with atmospheric oxygen[10] in alkaline solution with re-formation of the dyestuff *(1)*.

Investigations of the dependence of the reaction on structural features of the molecules are in progress. It is expected that the influence of the nitro group in *(1)* and the formation of the hydrogen bond in *(3)* are prerequisites for the reaction.

Experimental

The dye *(1)* (1 g)[1] ($\lambda_{max} = 537$ nm, $\varepsilon = 4.3 \times 10^4$ in acetonitrile) is refluxed for 2 h with anhydrous benzylamine (40 ml). After cooling, the mixture is acidified with 20% hydrochloric acid, and the benzaldehyde is removed by steam distillation and converted into its 2,4-dinitrophenylhydrazone which was identified by a mixed melting point with an authentic sample and by its IR spectrum. The imine *(3)* was precipitated from the residue by basification with 4 N sodium hydroxide solution [m.p. 295°C (acetonitrile). $\lambda_{max} = 420$ nm, $\varepsilon = 1.0 \cdot 10^4$ in acetonitrile (yield 65%)].

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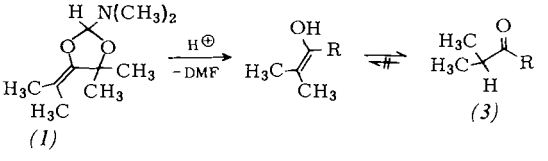
A Simple Dialkylated Enol[**]

By *H. M. R. Hoffmann* and *E. A. Schmidt*[*]

The reaction of 4-isopropylidene-5,5-dimethyl-2-dimethylamino-1,3-dioxolane *(1)* with weak acids has recently been shown to produce trialkylated enols of general structure *(2)*. Under favorable experimental circumstances these thermodynamically unstable compounds were obtained not only in substantial concentrations (up to 1 M), but also found to survive up to 3 weeks at room temperature before rearrangement into the corresponding ketone *(3)* was complete[1].



(2a), R = $C(CH_3)CH_2$ *(2c)*, R = $C(CH_3)_2OAc$
(2b), R = $C(CH_3)_2OCH_3$ *(2d)*, R = $C(CH_3)_2OH$

In view of the surprising kinetic stability of these enols the question is inevitable whether other enols, which are structurally even more simple, can be generated and identified under these conditions. A suitable precursor for such a study appeared to be 4-ethylidene-5,5-dimethyl-2-dimethylamino-1,3-dioxolane *(4)*, since it contains one methyl group less than its homolog *(1)*.

When *(4)*[2] was allowed to react with weak anhydrous acids under conditions previously shown to be optimum for obtaining the fully alkylated enols *(2)* the results were disappointing. For instance, treatment of a 1.1 M solution of *(4)* in CCl_4 with a 0.3 M equivalent of *tert*-butyl alcohol gave the α-amino ether *(6)* (80%) after 8 days at room temperature, and after another 14 days the 3(2*H*)-furanone *(7)*[4] was formed as the ultimate product. In commercial dimethyl sulfoxide (DMSO), which has proved a useful solvent for stabilizing transient enols[1], the rearrangement into *(7)* was found to be much more rapid, being complete after the solution of *(4)* had been left overnight at room temperature. Apparently, the potential enolate moiety of *(4)* is more nucleophilic and less basic than that of *(1)*;

[1] We thank Farbenfabriken Bayer AG for supply of a sample.
[2] We thank Prof. *H. Budzikiewicz*, Köln, for measurement of the spectra.

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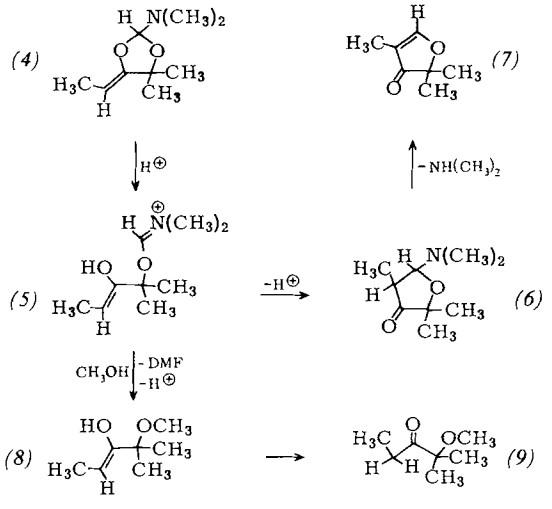
as a consequence, intramolecular alkylation of carbon with formation of *(6)* will be facile, especially in a polar aprotic solvent such as DMSO.



Interestingly, the reactions of heterocycle *(4)* proved to be very sensitive to the experimental conditions. Whereas a 1.1 M solution of *(4)* and catalytic amounts of benzoic acid (2.5×10^{-3} mol/l) at three different temperatures (−5, 27, 37 °C) gave the α-amino ether *(6)* once more, addition of two equivalents of methanol to *(4)* at 10 °C reduced the amount of *(6)* formed to 40% and gave 2-methoxy-2-methyl-3-pentanone *(9)*[5] as the major product (60%). In all experiments the formation of *(9)* was accompanied by release of an equimolar amount of dimethylformamide (DMF). Monitoring of the reaction by NMR was relatively difficult, since the spectra changed quickly and in addition to the starting material *(4)* and methanol, several compounds were present and formed simultaneously including *(6)*, *(9)*, and DMF. However, by scanning consecutive spectra, the rise and decline of three singlets at δ = 1.26 (6H), 3.08 (3H), and 7.00 ppm (1H) could clearly be discerned. As these signals disappeared, those of the ketone *(9)* grew in intensity. The comparison of the observed fleeting pattern with that of compound *(2b)*[1b] established beyond doubt that the intermediate was the enol *(8)*, the concentration of which reached a maximum (0.1 M)[6] after 10 min, then remained nearly constant for another 5 min while all precursor *(4)* disappeared. Only after *(4)* had vanished completely did the concentration of enol decrease; after a further 15 min rearrangement into the ketone *(9)* was generally complete.

When the same reaction was carried out at higher temperature (37 °C instead of 10 °C), the proportion of enol formed was actually greater (75% in place of 60%). Presumably, cleavage of the additional σ bond in going from *(5)* to the desired enol *(8)* requires a higher activation energy than closure to heterocycle *(6)*. However, the enol was more short-lived at the higher temperature as expected, reaching its maximum concentration after 5 min and disappearing completely after 15 min.

Treatment of *(4)* (1.1 M solution in CCl_4) with two equivalents of *O*-deuteriomethanol at 37 °C furnished the α-amino ether *(6)* (35%) and the *O*-deuterioenol *(8)-D* [NMR *inter alia* δ = 1.26 (s/6H), 3.07 (s/3H)], which rearranged into the corresponding deuterioketone *(9)-D*[7] (65%). In this instance the enol was sufficiently long-lived to reach a maximum concentration of 0.2 mol/l.

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[1] a) *H. M. R. Hoffmann* and *E. A. Schmidt*, J. Amer. Chem. Soc. *94*, 1373 (1972); b) *E. A. Schmidt* and *H. M. R. Hoffmann*, *ibid.* *94*, 7832 (1972).

[2] Prepared as described in Ref. [3]. The residual DMF (*ca.* 25%) can be removed conveniently by freezing it out at −78 °C from the pentane extract of the mother liquor. All operations must be carried out under thoroughly dry, deoxygenated nitrogen.

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[5] NMR spectrum of *(9)*: (TMS, CCl_4) δ = 0.99 (t/3H, *J* = 7 Hz), 1.21 (s/6H), 2.52 (d/2H, *J* = 7Hz), 3.13 ppm (s/3H). IR ν (CCl_4): *inter alia* 1710, 1470, 1370, 1180, 1070, 1045 cm^{-1}.

[6] The maximum concentration of the enols was calculated from peak heights, since the fast reactions did not permit integration between recordings.

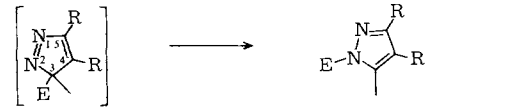
[7] NMR spectrum of *(9)-D*: (TMS, CCl_4) δ = 1.17 (d/3H, *J* = 7Hz), 1.22 (s/6H), 2.8 (mainly obscured by DMF), 3.15 (s/3H).

1,3-Dipolar Addition of Cyclic Diazo Ketones to Alkynes and Cyclopropene. Synthesis of Heterocycles by [1,5]-Acyl Migration

By *Michel Franck-Neumann* and *Christiane Buchecker*[*]

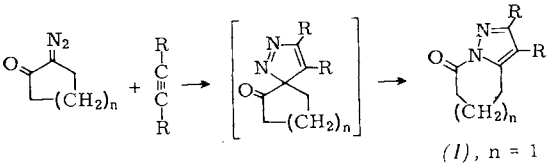
Dedicated to Professor Rudolf Criegee on the occasion of his 70th birthday

We recently found[1] a spontaneous [1,5]-group migration by which 3-acyl-, 3-alkoxycarbonyl-, or 3-cyano-3*H*-pyrazoles were converted into *N*-substituted pyrazoles at room temperature.



R = CO_2CH_3, E = $COCH_3$, $CO_2C_2H_5$, CN

These results have led us to a new synthesis of heterocycles. Cyclic α-diazo ketones such as 2-diazo-cyclopentanone or -hexanone[2] react with dimethyl acetylenedicarboxylate in boiling benzene to give *(1)* (m.p. 109 °C) or *(2)* (m.p. 82 °C), respectively, directly; the 3*H*-pyrazoles formed as intermediates were not isolated.



(1), n = 1
(2), n = 2

In these cases the acyl group is compelled to migrate directly to the nearest nitrogen atom since other possibilities (1,3-shift to N-1 or multiple 1,5-shifts over C-4 and C-5) would contradict Bredt's rule.

Bridged cyclic α-diazo ketones such as diazonorbornanone[3] and diazocamphor[4] react similarly but more slowly to give *(3)* (5 hours' heating in benzene, 63%

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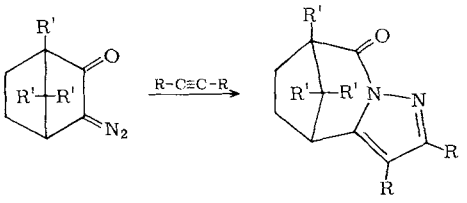
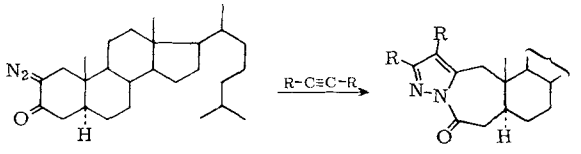
yield, m. p. 106 °C), and *(4)* (125 hours' heating in benzene, 73% yield, m. p. 86 °C), respectively.



(3), R' = H
(4), R' = CH_3

Steroidal diazo ketones also undergo this rearrangement. Thus in 2 h at 40 °C, 2-diazo-5α-cholestan-3-one[5] and a large excess of dimethyl acetylenedicarboxylate afford the steroidal pyrazole *(5)* (m. p. 204 °C) in 61% yield.

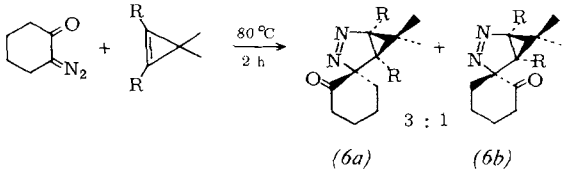


(5)

The heterocycles *(1)*—*(5)* form colorless crystals and show no N=N absorption in the ultraviolet region but only a shoulder at 235 nm (ε = 6000—7000). The NMR spectra (δ/TMS) of *(1)*, *(2)*, and *(5)* indicate two different methyl ester groups (two singlets near 3.90 ppm) and one CH_2 group α to the amide and another α to the pyrazole: *(1)* 2.77 and 3.38 ppm (broad triplet, $J = 6$ Hz); *(2)* 2.96 and 3.35 ppm (complex multiplet); *(5)* strongly shielded protons at 3.0 and 3.5 ppm (4 H), together with the typical steroid portion of the spectrum.

The spectra of the bridged heterocycles *(3)* and *(4)* resemble those of *(1)* and *(2)*, each having only two or one CH group: *(3)* 3.44 and 4.24 ppm (complex multiplets); *(4)* 3.79 ppm (1 H, broad doublet, $J = 6$ Hz).

Since cyclopropanopyrazolines resemble 3*H*-pyrazoles[6], we have also used a cyclopropene which is very reactive in 1,3-dipolar cycloadditions[7] (benzene solution). In this case the reaction stops at the primary products *(6a)* and *(6b)*. The total yield amounts to 70%. The main isomer *(6a)* (m. p. 99 °C) can be obtained pure by recrystallization from ether/light petroleum.



(6a) *(6b)*

In its NMR spectrum, *(6a)* ($\lambda_{max} = 335$ nm, $\varepsilon = 150$; $\nu(N{=}N) = 1540\ cm^{-1}$) shows two different methyl ester groups (3.72 and 3.88 ppm) and two methyl groups attached to the three-membered ring (singlets at 0.56 and 1.55 ppm). *(6b)* differs in its NMR spectrum only in respect of the signal of a methyl group attached to the three-membered ring (0.95 instead of 0.56 ppm).

With *(6a)* and *(6b)* no acyl group migration occurs; when warmed above 100 °C both isomers lose nitrogen quantitatively with formation of isomeric $C_{15}H_{20}O_5$ compounds.

This [1,5]-acyl migration, which is the basis of the heterocycle synthesis described here, thus occurs only when aromatization to a pyrazole is possible.

Dimethyl 8,11,11-trimethyl-7-oxo-5,6-diazatricyclo-[6.2.1.$0^{2,6}$]undeca-2,4-diene-3,4-dicarboxylate (4):

Diazocamphor (3.56 g, 20 mmol) and dimethyl acetylenedicarboxylate (2.82 g, 20 mmol) are mixed in benzene (45 ml) and heated under reflux for 125 h. After removal of the solvent the residue is taken up in ether/light petroleum (1:1) and chromatographed on silica gel (40 g). The first fractions (starting material) are followed, on elution with ether/light petroleum (3:1), by colorless, viscous, analytically pure *(4)* (4.70 g). Crystallization is effected by dissolution in diisopropyl ether and evaporation of the solvent.

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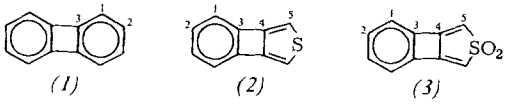
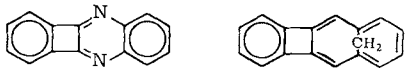
^{13}C Shifts in Biphenylene and Analogous Compounds[1]

By *Alan J. Jones*, *P. J. Garratt*, and *K. Peter C. Vollhardt*[*]

Recent observations that diamagnetic ring current contributions to ^{13}C shifts are insignificant relative to total range[2] suggest that the so-called paramagnetic ring current contribution to ^{13}C shifts in biphenylene *(1)*[3] be reassessed. It is our contention that an isolated molecule such as biphenylene cannot be used as a model to assess the paramagnetic ring current effect. A more correct approach is to compare the difference in chemical shifts for systems in which the current may be "*on*" or "*off*", and between which geometry does not unduly differ[2]. With the advent of syntheses for the biphenylene analogs *(2)*—*(5)*[4-7] these criteria could be satisfied. Our particular interest is, therefore, in benzocyclobuta[1,2-*c*]thiophene *(2)*, (2-thianorbiphenylene)[4], and its dioxide, the sulfone *(3)*. Com-



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



(4) *(5)*

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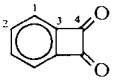
pound *(2)* is isoelectronic with biphenylene. Relative to the potential cyclobutadiene ring *(1)*, compound *(2)* therefore represents the "current-on" and compound *(3)* the "current-off" case, respectively.

The ^{13}C chemical shifts[8] of the compounds *(1)*—*(3)* are given in Table 1 along with supporting data on the model compounds *(6)*—*(8)*.

(6)

(7)



(8)

Table 1. ^{13}C chemical shifts in biphenylene and related compounds [a]. Unless indicated otherwise, assignments were confirmed using conventional techniques [9].

Compound	C-1	C-2	C-3	C-4	C-5	Total range of chemical shift
(1)	117.8_3	128.4_7	151.7_7			33.9_4
(2) [b]	118.1_3	128.4_4	145.5_6	146.6_8	112.5_1	34.1_7
(3) [c]	134.3_0	124.7_5	145.2_4	142.3_4	111.9_0	33.3_4
(6)	122.2_9	126.5_0	146.3_1	33.0_7		24.0_2
(7)	145.8_7		149.7_6		94.5_6	
(8)	135.4_5	122.3_7	173.2_0	194.2_8		

[a] All spectra were determined for solutions in deuteriochloroform. Shifts are given relative to internal TMS.

[b] Assignment of C-1 and C-2 is made by analogy with biphenylene. C-3 and C-4 are not distinguished.

[c] Assignment of C-1 and C-2 is based on analogy with the dione *(8)* and styrene. C-3 and C-4 are not distinguished.

A number of features in these data should be noted. (a) The remarkable similarity in the ^{13}C shifts and their total range[10] exhibited by the potential $4n\pi$-cyclobutadiene type molecules *(1)* and *(2)*. (b) The above similarity in shift range does not differ significantly in the cyclobutane-substituted benzenes *(3)* and *(6)*. (c) The shifts of the quaternary carbon, C-3, common to the junction of the benzene and four-membered rings in *(1)*, *(2)*, *(3)*, and *(6)* are similar (average value 147.2 ppm) and resemble that for the C-3 carbon in 3,4-dimethylenecyclobutene *(7)* (149.8 ppm). Finally, (d) the similarity in the shift at C-5 in *(2)* and *(3)* warrants consideration.

The similarity in the ^{13}C shifts and ranges in *(1)* and *(2)* suggest close electronic resemblance and justify our comparison of *(1)* and *(2)* with *(3)*. Other similarities noted in (b) through (d) suggest that we consider the data in terms of substituent additivity effects. It is clear that the low field shifts (average value 148.0 ppm) at the quaternary centers C-3 and C-4 in *(1)* and *(2)* are *not* exceptional, since the parent compound *(6)*, the sulfone *(3)*, and the dimethylenecyclobutene *(7)* exhibit similar shifts (average value 147.1 ppm). However, the upfield shifts (5—6 ppm) at C-4 in *(3)* compared to *(2)* and the high field shift at C-5 in *(3)* (111.9 ppm), which is similar to that for the analogous position in styrene (113.6 ppm)[11], do suggest that the 4,5-bond may be relatively localized in *(3)*.

Considering benzocyclobutene *(6)* as the parent compound for this series it is instructive to compare the shifts for the carbon atoms C-1 and C-2 in *(1)*, *(2)*, *(3)*, and *(8)*. Thus, upfield shifts (4.5 and 4.2 ppm) and downfield shifts (2.0 and 1.9 ppm) occur at C-1 and C-2 in compounds *(1)* and *(2)*, respectively. In compounds *(3)* and *(8)* downfield shifts (12.0 and 13.2 ppm) and upfield shifts (1.7 and 4.1 ppm) occur at C-1 and C-2, respectively. These comparisons, and the earlier considerations relating to C-3 and C-5 in *(3)* lead to the suggestion that the compounds *(3)* and *(8)* are electronically similar and, consequently, that they may be considered as benzocyclobutenes substituted by relatively localized double bonds at C-4.

It remains to reconcile the chemical shifts between the compounds *(2)* and *(3)*. The similarity noted in the shifts at C-5 in *(2)* and *(3)* may be a consequence of either (i) that the double bonds in the heterocyclic ring of *(2)* are relatively localized, and *(2)* has substantial dimethylenecyclobutene character, or (ii) the presence of a paramagnetic shielding current in the four-membered ring of *(2)*, which effectively compensates for the diamagnetic current induced in the thiophene ring. This latter mechanism seems unfavorable since it is recognized[2, 12] that magnetic effects induced by diamagnetic currents change from deshielding to shielding immediately upon crossing from locations outside to locations inside the ring. Consequently, the diamagnetic contribution of the thiophene ring at C-5 is expected to be zero. The downfield shift at C-5 (0.6 ppm) in *(2)* compared to *(3)* is, therefore, in the wrong direction for an expected "dominant" paramagnetic effect. Further, cancellation of possible diamagnetic and paramagnetic effects in *(2)* would be expected to give rise to upfield shifts at both C-1 and C-2 in *(2)* compared to *(3)*. A large upfield shift (16.2 ppm) is observed at C-1 but the downfield shift (3.6 ppm) at C-2 cannot be reconciled with a ring current model.

We suggest, therefore, that the upfield shift at C-1 and the downfield shifts at C-2 and C-5 in *(2)*, as compared to *(3)*, are the consequence of some contribution from the delocalized thiophene structure to *(2)*. Further, the similarities and difference in shifts at C-1 through C-4 in compounds *(1)*, *(2)*, and *(6)* suggest that *(1)* and *(2)* are benzene and thiophene substituted benzocyclobutenes, respectively.

We conclude that additivity relationships account adequately for the ^{13}C chemical shifts in the compounds studied. On the basis of the similarities noted in (a) through (d) compounds *(1)* and *(2)* must be considered as annelated benzocyclobutenes, while *(3)* is a dimethylenebenzocyclobutene. However, it is noteworthy that all of the stable polycyclic systems containing a potential cyclobutadiene ring so far isolated [*e.g. (1)*, *(2)*, *(4)*, *(5)*] have the common feature of being able to accommodate the four-membered ring in either the dimethylenebenzocyclobutene or dimethylenecyclobutene form with only partial disruption of the aromatic system with which it is associated[13]. As expected this feature gives rise to a high reactivity in addition reactions[5]. The contrast provided by the proton chemical shifts in *(2)* and *(3)* may still be reconciled by the paramagnetic ring current postulate. However, the effect of this "current" on the ^{13}C shifts is considered to be insignificant (1—3 ppm) relative to the ^{13}C shift range[14].

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[1] Presented in part at the First Rocky Mountain Regional ACS Meeting, Colorado State University, June 1972.

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[8] Determined in the Fourier mode using a Bruker HFX-90 spectrometer operating at 22.63 MHz with a deuterium lock.

[9] For a summary see: *A. J. Jones, D. M. Grant*, and *K. F. Kuhlmann*, J. Amer. Chem. Soc. *91*, 5013 (1969).

[10] The total range of ^{13}C shifts is considered to reflect the extremes in charge distribution. Compared to other alternant hydrocarbons the shifts observed in these systems indicate that the charge is relatively localized.

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[12] *A. J. Jones, T. D. Alger, D. M. Grant*, and *W. M. Litchman*, J. Amer. Chem. Soc. *92*, 2386 (1970).

[13] See: *P. J. Garratt* and *K. P. C. Vollhardt*, J. Amer. Chem. Soc. *94*, 1022 (1972). The only compound for which this is not so is 6,7-diphenyl-3-thiabicyclo[3.2.0]heptatriene.

[14] A.J.J. thanks the National Research Council of Canada for financial support.

Does a "Ring Current Effect" Exist for ^{13}C-Nuclear Magnetic Resonance? A Study of Bridged Annulenes[**]

By *Harald Günther, Hans Schmickler, Heinrich Königshofen, Klaus Recker*, and *Emanuel Vogel*[*]

Theoretical studies and previous experimental evidence[1] show that the magnetic shielding constant σ of the ^{13}C nucleus is influenced mainly by the immediate electronic environment and by the paramagnetic contribution to the shielding[2]. Thus in ^{13}C-resonance spectroscopy only secondary importance attaches to the neighboring group effects (magnetic anisotropy, field and van der Waals effect) which are so important[3] for interpretation of the chemical shifts in proton resonance spectroscopy.

In annulene chemistry particular interest centers on the magnetic anisotropy of cyclic conjugated $[4n]$- and $[4n+2]$-π-electron systems which, as paramagnetic or diamagnetic (respectively) "ring current effect", now ranks as the most important physical characteristic of annulenes[4]. The increasing significance of ^{13}C-resonance spectroscopy for structural elucidation and characterization of unsaturated systems made it important to investigate the extent to which ring current effects influence chemical shifts of the ^{13}C nucleus, particularly as previous studies[5-8] failed to clarify this situation convincingly.

Particularly suitable for such an investigation are the bridged annulenes such as *(1)*, *(3)*, *(5)*, and *(8)*[9], whose bridging C atoms lie in the diamagnetic [*(1)*, *(3)*, *(5)*] or paramagnetic [*(8)*] region of the anisotropy cone of the π-electron cloud (Fig. 1)[10]. Since one cannot expect

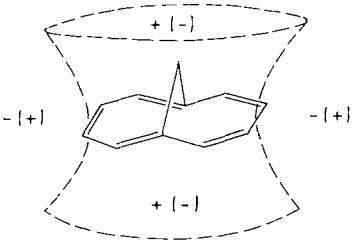

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Fig. 1. Diamagnetic (paramagnetic) ring current effect in bridged annulenes.

a comparison with substituent constants measured for open-chain[11,12] or alicyclic compounds[13] to reveal a possible ring current effect for ^{13}C-resonance, suitable reference compounds also have to be analyzed. In that respect, because of the sensitivity of ^{13}C-resonance to steric factors[1], it is important to choose systems that are closely related in their geometry to the annulenes in question. In the ideal case the only difference from the annulene should be the absence of a dia- or paramagnetic ring current. The present investigation, whose results are shown in Figure 2, is thus confined to the systems *(1)*—*(8)*[14]. Previous ^1H-NMR studies[15-17] enable us to start the present discussion from the fact that the [10]- or [14]-annulenes *(1)*, *(3)*, and *(5)* show a diamagnetic ring current effect whilst for the [12]annulene *(8)* the positions of the proton resonances [$\delta(H_{ring})=5.4$—5.8, and $\delta(CH_2)=6.1$ ppm] permit recognition of a paramagnetic ring current. Comparison with the model substances *(2)*, *(4)*, *(6)*, and *(7)* (for which no ring current is induced in the magnetic field) then shows (Fig. 2) that the strongest influence on the ^{13}C-resonance of all fully conjugated π-systems is due to strain effects arising on introduction of the remaining double bonds. This is already clear from the position of the ^{13}C signal in the spectrum of the 1,6-methano[10]annulene *(1)*[18]; here the absorption of the quaternary carbon atoms was found at highest field although, according to known substituent effects[11], these nuclei should experience the least shielding. The aromatization, *i.e.* conversion of *(2)* into *(1)*, thus leads to an upfield rather than a downfield shift of the C(c) resonance. Since such effects are known to extend over several C

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[**] Applications of ^{13}C-Resonance Spectroscopy, Part 3.—Part 2: *H. Günther, B. D. Tunggal, M. Regitz, H. Scherer*, and *T. Keller*, Angew. Chem. *83*, 585 (1971); Angew. Chem. internat. Edit. *10*, 563 (1971). We thank the Deutsche Forschungsgemeinschaft for a grant.

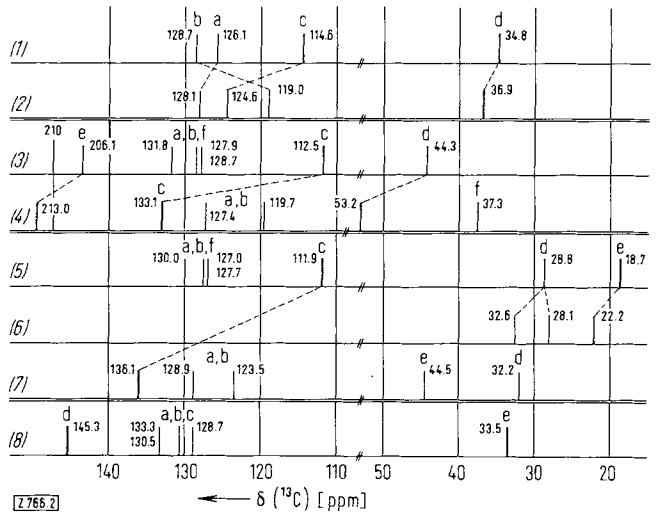

Fig. 2. Schematic representation of the ^{13}C-resonance spectra of the systems *(1)—(8)*. The ^{13}C-resonance in tetramethylsilane served as internal standard. Conditions of measurement: *(2), (5)—(7):* room temperature, in CCl_4; *(1):* room temperature, in CS_2; *(3), (4):* $-80\,^{\circ}C$, in CD_2Cl_2. Concentration in all cases *ca.* 1 mol/l or less. Experimentally proved assignments are denoted by thick lines.

atoms, sometimes with change of sign, it is impossible to reach a conclusion about the existence or non-existence of a diamagnetic ring current effect by means of the shifts for the other peripheral C atoms of which one pair is deshielded. Thus also the shielding observed for the methylene-carbon provides no information relevant to our problem.

For the pair of compounds *(3)/(4)* the influences of the geometrical changes expected with aromatization on the ^{13}C-resonance can be considered to be smaller than those for *(1)/(2)* since the structure of the periphery differs only little between the two systems. Thus the C=O stretching vibration, which is sensitive to angle deformation, is $1730\,cm^{-1}$ for both compounds[16]. Hence it is interesting that in this case—independently of the correct assignment—both the outer peripheral C atoms C(a) and C(b) are deshielded on going from *(4)* to *(3)*, whereas the same change produces considerable shielding of the bridging C atoms. For the carbonyl carbon, whose resonance should be least affected by other factors, one finds a shift of +7 ppm. This observation clearly provides positive evidence for the existence of a diamagnetic ring current effect on the ^{13}C-resonance[19].

This interpretation is supported by the results for the pair of compounds *(5)/(6)*. Here too the differences in geometry are certainly small, and the downfield shift of the bridging C atoms on transition from *(5)* to *(6)* can be ascribed to the decrease in the ring current effect that is unambiguously proved by ^1H-NMR investigations[20]. Only for the resonance of C(d') can (slight) shielding be observed, whose cause may be seen to lie in the anisotropy effect of the benzene ring. The corresponding proton is also strongly shielded. A ring current effect is further indicated by the fact that C(d) in *(5)* is shielded in comparison with C(d) in *(7)* to the extent of 3.4 ppm, for deshielding would normally be expected on replacement of a hydrogen atom by a CH_2 group[11,12].

On the other hand, no paramagnetic ring current effect could be demonstrated for the ^{13}C-resonances in the [12]annulene *(8)*. Here the methylene-carbon should be deshielded, yet no effect of this kind could be recognized either in comparison with the $[4n+2]$-π-system *(1)* or in that with the olefinic system *(2)*[21].

In conclusion, it can be stated that a diamagnetic ring current effect does exist also for the ^{13}C-resonances but that it is masked in most cases by other factors that affect the ^{13}C-resonance appreciably more strongly. No paramagnetic ring current effect could be detected in our case. These findings are in clear contradiction to the influence observed on ^1H-resonance, whose shift is unambiguously determined by the ring current effect for the pairs of compounds discussed here (Fig. 3). ^{13}C-resonance is thus not

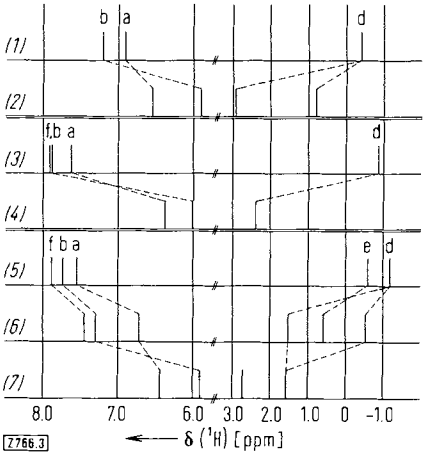

Fig. 3. Schematic representation of the ^1H-resonance spectra of the systems *(1)—(7)* (according to [15–17, 20, 22]).

suitable as a probe for the magnetic properties of cyclic π-systems. Incidentally our observations confirm other findings[1], according to which steric effects such as ring strain and angle deformations play a dominant role in determining the position of the ^{13}C-resonance signals[23].

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[10] No theoretical prediction does exist for the sign of the induced secondary field at the position of the peripheral C atoms. Results for the ^1H-resonance cannot be simply adopted because of the different positions of the nuclei. The simple model of a current loop or coil (consideration of two ring currents corresponding to the π-electron distribution in the carbon-$2p_z$ orbitals) indicates that the secondary field on the carbon nucleus disappears for planar systems. Indications of the existence of a ring current effect are thus to be expected primarily from the resonances of the bridging C atoms.

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[17] *W. Bremser, J. D. Roberts*, and *E. Vogel*, Tetrahedron Lett. *1969*, 4307; *H. Günther, D. Cremer*, and *E. Vogel*, unpublished.

[18] The ^{13}C-spectrum of *(1)* was first measured by *W. Bremser* (*W. Bremser*, personal communication); more recently it has been measured by *S. Masamune et al.* (*S. Masamune*, personal communication).

[19] We were able to show that, at room temperature, *(4)* exists in valence-tautomeric equilibrium with the corresponding norcaradiene form. The ^{13}C-spectra of both isomers can be observed at $-80\,^{\circ}C$. To exclude temperature effects we measured the spectrum of *(3)* also at $-80\,^{\circ}C$ (CD_2Cl_2), but hardly any change from the room-temperature spectrum was found.

[20] *H. Günther, H. Schmickler, K. Recker*, and *E. Vogel*, unpublished work.

[21] The temperature-dependence of the ^1H-NMR spectrum of *(8)* (measured down to *ca.* $-80\,^{\circ}C$) indicates that a double-bond shift occurs in this molecule. This should have little or no effect on the position of the ^{13}C-resonances.

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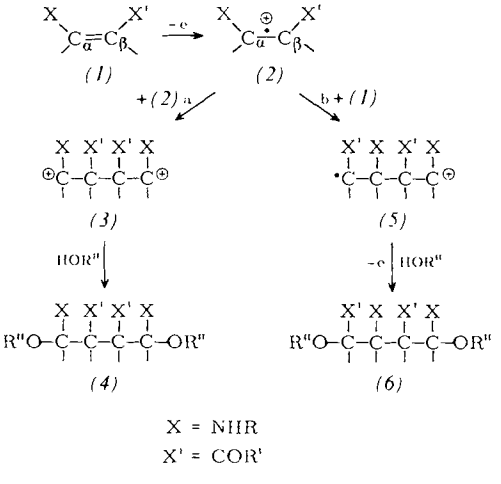
[23] *Note added in proof* (March 19, 1973): *R. H. Levin* and *J. D. Roberts*, Tetrahedron Lett. *1973*, 135, have just reported on a weak diamagnetic ring current contribution to the ^{13}C resonance frequency of some CH_2 groups in [12]paracyclophane.

One-Step Synthesis of Pyrroles by Anodic Dimerization of Enamino Ketones or Esters[**][1]

By *Dietrich Koch* and *Hans Schäfer*[*]

Anodic dimerization has previously been achieved only for olefins with electron-donating substituents[2]. We have now electrolyzed vicinally disubstituted olefins *(1)* with one electron-donating (X) and one electron-attracting substituent (X'), in order a) to extend the preparative usefulness of the dimerization and b) to decide, from the structures of the dimers, whether the C—C linkage by way of the radical cation *(2)* occurs by radical dimerization (route a) or by electrophilic addition (route b).



Route a should lead to the dication *(3)* in which the two positive charges are stabilized by the substituents X; solvolysis of *(3)* should afford the symmetrical dimers *(4)*. The radical cation *(5)* should be formed by route b[3], and its oxidation and solvolysis should lead to the unsymmetrical dimers *(6)*.

For the enamino ketones or esters *(1a)—(1e)* the half-wave potentials on voltammetry in a methanolic $NaClO_4$ solution at a rotating vitreous carbon or gold electrode are found between +1.0 and +1.2 V (*versus* Ag/AgCl). Controlled-potential preparative electrolysis at graphite electrodes yields the pyrroles *(7a)—(7e)* (Table 1).

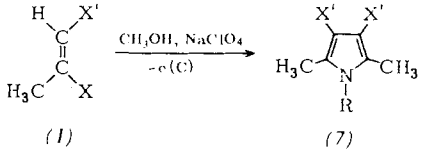
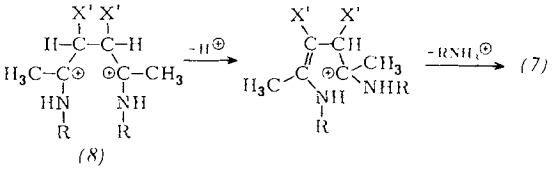


Table 1. Yields and melting points of the pyrroles *(7)* prepared from *(1)*.

	X	X'	R	*(7)* [a] M.p. [°C]	Yield [%] [b]
a	NH_2	CO_2CH_3	H	120—121 (118—119[6])	34 (22)
b	$NHCH_3$	CO_2CH_3	CH_3	149.5—150	36 (33) [c]
c	NH_2	$COCH_3$	H	178—179 (180—181[7])	16 (15)
d	$NHCH_2C_6H_5$	CO_2CH_3	$CH_2C_6H_5$	105—106	45 (47)
e	NHC_6H_5	CO_2CH_3	C_6H_5	86—87 (87—88[8])	12 (9)

[a] The structures of the pyrroles are proved by IR, NMR, and mass spectroscopic data, as well as by C,H analyses and comparison of the melting points with those of authentic compounds.
[b] The yields of the pyrroles *(7)* separated by thin-layer chromatography relate to the amounts of olefin *(1)* used (material yields); the figures in parentheses are current yields. Electrolysis and workup conditions were not optimized.
[c] In dichloromethane/methanol (20:1, v/v).

Formation of the symmetrically substituted pyrroles indicates radical dimerization of the radical cations (route a) formed as primary products from *(1a)—(1e)*. This process leads to the dications *(8)* from which the pyrroles *(7)* can be formed by cyclization and elimination of amine.



This new pyrrole synthesis supplements their preparation by 1,3-dipolar cycloadditions of azlactones to alkynes[8,9].

Dimethyl 1-benzyl-2,5-dimethyl-3,4-pyrroledicarboxylate (7d):

Methyl 3-(benzylamino)crotonate (19.5 g, 95 mmol) is electrolyzed in 0.3 N methanolic $NaClO_4$ solution (45 ml) with

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benzene (3 ml) to aid dissolution, at graphite electrodes (P 127, Sigri, Meitingen), at +10 °C, with an anode potential of +0.95 V (*versus* Ag/AgCl) and a current density of 57 mA/cm², up to consumption of 90 mF. On preparative thin-layer chromatography (benzene/ether 10:1 v/v) the crude product (600 mg) afforded the product *(7d)* (210 mg).

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[3] According to the ESR spectra [4], the lone electron in the radical cations of enamines is localized in the β-position, and the positive charge in the α-position to $X=NR_2$. Further, since enamines are more nucleophilic at C_β than at C_α [5], C_α of *(2)* adds electrophilically to C_β of *(1)*.

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Polyvinyl Alcohol Substituted by Nucleotides as Carrier for Liquid Phase Oligonucleotide Synthesis[**]

By *Herbert Schott*[*]

Polystyrenes[2], polyethylene glycols[3], and Sephadex LH 20[3] have been used as carriers in the synthesis of oligonucleotides by *Merrifield*'s method[1]. The nucleotide chain remains bound to polystyrene during the synthesis by means of trityl or benzyl groups[4]; in polyhydroxy compounds covalently bound 5'-ribonucleotides serve as anchors. Polyhydroxy compounds can be more easily obtained than polystyrene carriers and have the advantage of an almost complete absence of the side reactions observed with polystyrenes, particularly during removal of the chain[5]. Since the maximum loading of the carriers named above is about 0.3 mmol of nucleotide per gram of polymer, oligonucleotide syntheses have thus far been practicable only in μmol batches.

We have now found that one gram of polyvinyl alcohol can be loaded with up to 10 mmol of mononucleotide. Polyvinyl alcohol is soluble in mixtures of pyridine and hexamethylphosphorotriamide. Condensations in the presence of this latter amide have been described[6]. Thus all reactions with this carrier can be carried out in the liquid phase.

For condensation with the carrier we used 5'-thymidyl-, 5'-uridyl-, or 5'-ribo-guanylic acid in a protected form and, after completion of the reaction, removed the protecting groups by short treatment with alkali. The condensations were carried out by means of 2,4,6-triisopropylbenzenesulfonyl chloride (TPS) in hexamethylphosphorotriamide/pyridine and produced more than 90% yields. For removal of lower-molecular products and unattached nucleotides the reaction mixture can be dialyzed, precipitated, or separated by column chromatography on Sephadex or DEAE-cellulose. Substituted polyvinyl alcohol passes through a Sephadex-G-50 column in the eluant and is bound to DEAE cellulose as a polyanion. Retardation is so strong that complete elution is only possible with 7 M urea/1 M sodium chloride. The column-chromatographic separations prove indirectly the covalent bonding of the nucleotides and permit unbound nucleotides to be recovered. The nucleotide content of the dissolved polymers can be determined by UV measurements and checked gravimetrically on precipitated material.

Experimental:

Polyvinyl alcohol (1 g, MW *ca.* 70000) is dissolved with stirring in hot anhydrous hexamethylphosphorotriamide (40 ml). Anhydrous pyridine (40 ml) is added to the clear, pale yellow solution which is then cooled to room temperature. Subsequently pyridinium 2',3'-di-*O*-acetyluridine 5'-phosphate (5 g, *ca.* 10 mmol) is added to the mixture, followed by TPS (9 g, *ca.* 30 mmol), with continuous stirring. After this mixture has been stirred for 24 h at room temperature, water (10 ml) is added and the whole is dialyzed for 12 h against water. For removal of the protecting groups sodium hydroxide solution is added until a 1 M NaOH solution results. After standing for 10 minutes at room temperature the solution is neutralized with HCl and then concentrated in a vacuum to a syrup from which the polymer is precipitated by addition of ethanol (*ca.* 200 ml). The precipitate is dissolved in water and dialyzed for 12 h against water. 97000 absorption units were measured in the dialyzed solution by spectral photometry (262 nm). The extinction ratios were 250/260 = 0.85 and 280/260 = 0.32. The solution is concentrated in a vacuum and lyophilized, yielding a yellow powder (4.1 g).

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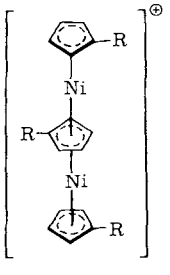
Preparative and Mechanistic Aspects of the Reactions of Cyclopentadienylmetal Complexes: The Route to the Triple-Decker Sandwich

By *Helmut Werner*[*]

Reactions of sandwich complexes of the type $M(C_nH_n)_2$ ($n = 5$ or 6) with Lewis acids and Lewis bases have attracted increasing interest in recent years[1]. Marked reactivity is exhibited by compounds such as $Co(C_5H_5)_2$ and $Ni(C_5H_5)_2$ in which the metal atom possesses a formal excess of one or two electrons, respectively, beyond the 18 electron shell (noble-gas configuration).

The action of *Lewis bases* [*e.g.* tertiary phosphites $P(OR)_3$] on the above-mentioned bis(η-cyclopentadienyl)metal compounds can lead to fission of only *one* metal-ring bond or to fission of *both* $M—C_5H_5$ bonds[2, 3]. Products are formed such as $C_5H_5Co[P(OR)_3]_2$ and $Ni[P(OR)_3]_4$ which can undergo unexpected reactions on thermolysis. Mechanistic studies of the reaction of $Ni(C_5H_5)_2$ and $P(OR)_3$ have led to isolation of compounds such as $Ni(C_5H_5)_2 \cdot MA$ (MA = maleic anhydride), $C_5H_5Ni[P(OR)_3]Cl$, and $C_5H_5Ni[P(OR)_3]P(O)(OR)_2$.

The behavior of $Co(C_5H_5)_2$ and $Ni(C_5H_5)_2$ towards *Lewis acids* is characterized by a one-electron transfer as primary step[4]. $Co(C_5H_5)_2$ reacts with $[C(C_6H_5)_3]^+$, $[C_7H_7]^+$, or H^+ (as HF or HBF_4) very rapidly with formation of the stable cation $[Co(C_5H_5)_2]^+$[5]. The less stable cation $[Ni(C_5H_5)_2]^+$ undergoes subsequent reactions that lead under suitable conditions to the binuclear complex $[Ni_2(C_5H_5)_3]^+$[6]; its formation is very probably to be interpreted in terms of an ion-molecule reaction. Ring-substituted derivatives $[Ni_2(C_5H_4R)_3]^+$ (R = CH_3 or *tert*-C_4H_9) are also very easily obtained from the system $Ni(C_5H_4R)_2/HBF_4$/propionic anhydride[7]. Both spectroscopic data and chemical properties of the complex cations $[Ni_2(C_5H_4R)_3]^+$ indicate that these represent a new structural type *(1)*, which in accord with previous proposals[8] we name "triple-decker sandwiches".



(1)

The reactions of the complexes $[Ni_2(C_5H_4R)_3]BF_4$ with a series of uni- and multi-dentate Lewis bases L or L—L afford quantitative yields of $Ni(C_5H_4R)_2$ and new ionic mono(η-cyclopentadienyl)nickel compounds $[C_5H_4RNiL_2]BF_4$ or $[C_5H_4RNi(L—L)]BF_4$[9, 10], of which the representatives with L—L = diolefin are worthy of particular mention.

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Prebiotic Evolution of Enzyme-Like Systems

By *Klaus Dose*[*]

Model experiments have indicated that the lower-molecular building units of the first living systems could have arisen by the action of various forms of energy (electric discharges, solar UV light, ionizing radiation, volcanic heat) on the components of the primitive atmosphere of the primordial earth. This secondary atmosphere was of volcanic origin and probably contained the elements C, H, O, N, and S, mainly in the form of CO_2, CO, CH_4, H_2O, N_2, and H_2S. Thus the composition of this atmosphere was different from that of the H_2- and He-rich intergalactic cloud from which our solar system was formed almost 5 billion years ago. Free oxygen was formed in the terrestrial atmosphere only in the last 3 billion years, after the appearance of photosynthetic organisms. Substantial (chemical) evolution of biologically important compounds in an oxidizing atmosphere cannot occur under prebiotic conditions.

α-Amino acids usually predominate in the products formed by the action of energy on various simulated primitive atmospheres. It is assumed that they are formed mainly by hydrolysis of racemic α-amino nitriles that are obtained as intermediates from aldehydes, HCN, and NH_3. Mixtures of α-amino acids, particularly when containing substantial proportions of acidic amino acids, can condense to protein-like polymers (proteinoids) when heated for several hours at 100 to 185 °C. These proteinoids give a positive biuret reaction and yield free amino acids on hydrolysis. Proteinoids are, however, only partially degraded by proteases since they contain non-physiological cross-linkages. Remarkable is the selectivity with which the amino acids condense to specific kinds of proteinoid with definite structures (small range of molecular size and charge distribution). The proteinoids have various catalytic properties.

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For instance, proteinoids have been synthesized that accelerate the decarboxylation of pyruvate or oxaloacetate. Catalysis of hydrolyses (of esters), reductive aminations (of α-keto acids), oxidative deaminations (of α-amino acids) and peroxidatic reactions were also observed. Peroxidatic activity [oxidation of an (organic) substrate by H_2O_2] is shown by proteinoids that are linked with hemin. These hemoproteinoids may have made possible a first oxidative metabolism at a time when the atmosphere was still oxygen-free; the H_2O_2 necessary for this process could have been continuously regenerated by the action of UV light or ionizing radiation on the primitive hydrosphere.

Lecture at Saarbrücken, July 7, 1972 [VB 357 IE]
German version: Angew. Chem. *85*, 231 (1973)

ABSTRACTS

Reviews

Abstracts of selected progress reports and review articles

The mechanisms of stepwise electrode processes on amalgams are the subject of a review by *V. V. Losev*. The author presents a complete kinetic analysis of anodic dissolution and cathodic deposition of metals forming multiply charged ions so that charge transfer is a stepwise process involving intermediates bearing lower charges. Experimental difficulties attending work with solid metal electrodes are obviated with amalgams, thus accounting for the interest they attract. [Mechanisms of Stepwise Electrode Processes on Amalgams. Mod. Aspects Electrochem. *7*, 314—398 (1972); 179 references]

[Rd 556 IE—G]

The use of isotopes for kinetic studies of heterogeneous catalysis is the subject of a review by *J. Happel*. The author considers publications concerned with chemisorption, the reaction itself, and subsequent desorption, *i.e.* mass transfer and diffusion processes preceding and following these steps are not included. The results are illustrated with the aid of NH_3 synthesis, SO_2 oxidation, oxidation of CO to CO_2, and hydrogenation and dehydrogenation of C_4 hydrocarbons. [Study of Kinetic Structure Using Marked Atoms. Catal. Rev. *6*, 221—260 (1972); 100 references]

[Rd 559 IE—G]

Conformational changes and thermodynamic properties of macromolecules in ternary polymeric systems is the subject of a review by *A. V. Gevarkyan*. The author summarizes the previously reported properties of polymers in binary solvent mixtures and tries to explain a few of the anomalies between theory and experiment. Conformational changes of the macromolecule, especially the transformation from the "random form" to the "segregated form", are discussed in relation to the composition of the solvent. [Conformational and Thermodynamic Properties of Macromolecules in Ternary Polymeric Systems. Russ. Chem. Rev. *41*, 216 to 221 (1972); 61 references]

[Rd 586 IE—Q]

Loading of the Rhine with organic, especially petrochemical, pollutants is discussed in a review by *W. Kölle, H. Ruf*, and *L. Stieglitz*. An overall estimate of pollution by organic pollutants can be gained from measurement of the oxygen demand per 1 mg of organically bound carbon. Most of the substances responsible for pollution can also be determined UV spectroscopically. Radiocarbon dating can be used as an analytical method for overall assessment of pollution and for differentiation between biogenic substances and substances of petrochemical origin. Biogenic substances can be readily monitored and dated according to their ^{14}C activity whereas fossilized petrochemical substances possess practically no such activity. Traces of organic substances can be determined by a combination of mass spectrometry and gas chromatography. Approximately 100 readily extractable and vaporizable compounds (isomers not considered!) have so far been identified. The enrichment of pollutants (*e.g.* by plankton, fishes, fish-eating birds) has also been monitored. The Hg-content of fishes taken from the Rhine near Mannheim considerably exceeds the tolerated limit of 0.5 ppm for human consumption. The fish lipoid fraction contains about 200 ppm of organically bound chlorine. [Die Belastung des Rheins mit organischen Schadstoffen. Naturwissenschaften *59*, 299—305 (1972); 15 references]

[Rd 594 IE—M]

The intermediary metabolism of mycobacteria is the subject of a review by *T. Ramakrishnan, P. S. Murthy*, and *K. P. Gopinathan*. These bacteria, which resemble one another primarily in their cell wall structure, are of interest because they include pathogenic organisms. The long generation times make working with them a little difficult; nevertheless, numerous studies have been carried out on their carbohydrate and lipid metabolism. Hopes of finding variations in metabolism associated with virulence were not fulfilled; such differences are found, however, in the enzyme complement although their significance is not yet understood. Protein and nucleic acid synthesis are being investigated mainly with a view to the use of drugs; the studies are still in their infancy. The metabolism of the vitamins, which could also offer therapeutic points of attack, known modes of action of drugs, and the genetics of mycobacteria close the article. [Intermediary Metabolism of Mycobacteria. Bacteriol. Rev. *36*, 65—108 (1972); 436 references]

[Rd 547 IE—R]

The chemistry of filling materials used in dentistry is the topic of a review by *G. M. Brauer* and *E. F. Huget*. The authors show that the ideal material is not yet available for conservative dentistry since all substances used (metals, metal alloys, synthetic resins, ceramic masses, and organic/inorganic mixed phases) are held in place in the dental cavity by mechanical forces but do not undergo chemical bonding to the teeth. Such a material would be most welcome as it would greatly reduce the incidence of secondary decay and its use would reduce losses of healthy dental material during treatment. However, lack of effective *in vitro* methods for testing its suitability means that an essential prerequisite for the development of such an adhesive is not fulfilled. [Dental Adhesives. Chem. Biosurfaces *2*, 731—800 (1972); 179 references]

[Rd 553 IE—G]

The growth of mammalian cells on glass surfaces is reviewed by *C. Rappaport*. It has been known since the 1930's that some kinds of cells can grow *in vitro*, *i.e.* on glass surfaces, and modern biology makes extensive use of such cell cultures. Other kinds of cells, particularly those regarded as specialized (brain cells, liver cells) resist attempts to culture them outside the body under such simple conditions. The reason is unknown, as are the conditions under which cells multiply in the body. The author surveys papers concerned with these problems. [Some Aspects of the Growth of Mammalian Cells on Glass Surfaces. Chem. Biosurfaces *2*, 449—487 (1972); 46 references]

[Rd 558 IE—G]

The determination of the number of active centers and growth rate constants in the catalytic polymerization of olefins is described in a review by *Yu. I. Ermakov* and *V. A. Zakharov*. The following methods for the determination of these growth characteristics are described and their reliability discussed: the kinetic method (investigation of the degree of polymerization as a function of reaction conditions), the inhibitor method (calculation of the number of active centers from the amount of inhibitor required to stop the reaction), and the labeling method (radioactive labeling of the growing molecule). Values of the growth factors are given for a few catalytic systems. Interesting conclusions regarding the mechanism of polymerization and the structure of the active centers can be drawn from the dependence of such values on the composition of the catalyst, its method of preparation, and the polymerization conditions. [Determination of the Number of Active Centres and Growth Rate Constants in the Catalytic Polymerization of α-Alkenes. Russ. Chem. Rev. *41*, 203—215 (1972); 113 references]

[Rd 585 IE—Q]

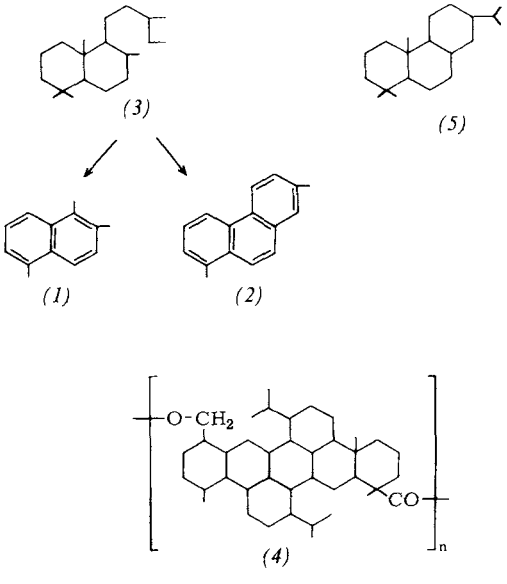
Thermogalvanic cells have been reviewed by *B. F. Markov* and *E. B. Kuzyakin*. In such cells, two identical electrodes at different temperatures are connected *via* a fused-salt electrolyte. The electromotive force of this element is a function of the temperature and the type of element. Here the authors concern themselves in particular with the theory and practice of thermogalvanic cells having metal- and halogen-electrodes and a single component fused-salt electrolyte. A few examples of how the observed characteristics and temperature dependence of the thermopotential can be utilized in the physical chemistry of fused salts are discussed. [Thermogalvanic Cells with a Single Fused Salt. Russ. Chem. Rev. *41*, 250—257 (1972); 47 references]

[Rd 588 IE—Q]

The analysis of hallucinogenic drugs is reviewed in an article by *A. Sperling*. New methods of analysis as well as old ones still in use are described. Chromatographic methods are particularly suitable. In fact, thin-layer and column chromatography are relatively inexpensive and rapid methods for the separation of LSD and LAA (lysergic acid amide). Thin-layer chromatography is used for the qualitative detection of the decomposition products formed by UV radiation; a quantitative determination can be carried out UV-spectrometrically at 312 nm. Few satisfactory results have so far been obtained with gas chromatography, whereas mass spectrometry has proved to be very useful since LSD shows three characteristic peaks ($m/e = 323, 221, 207$). Unfortunately, high investment costs restrict this method to forensic laboratories. Hallucinogenic tryptamines, such as α-methyl-, dimethyl-, diethyl-, and dipropyltryptamine are separated thin-layer chromatographically and developed by spraying with *p*-dimethylaminobenzaldehyde. This analysis could also be carried out gas chromatographically. Numerous hallucinogens can be determined by fluorescence, IR, NMR, and mass spectrometry. Several methods for the extraction of tetrahydrocannabinol are described. [Analysis of Hallucinogenic Drugs. J. Chromatogr. Sci. *10*, 268—275 (1972); 48 references]

[Rd 591 IE—X]

Amber. Recent research on amber is reviewed by *C. W. Beck*. Numerous secondary products are formed during the fractionation of the components of amber: dehydrogenation leads to agathalin *(1)* and pimanthrene *(2)*, thus indicating the presence of the diterpene of type *(3)*. Lambertinic acid and sciadopinic acid, which have been isolated from the Californian sugar pine and Japanese umbrella pine respectively, also belong to type *(3)*. Accord-



ing to another hypothesis, amber should basically contain a derivative of abietic acid, the polyester *(4)* according to *Rottländer* (model studies with diabietic acid). If such is the case the resin acid of amber would be of the type *(5)* and isopropyl groups should be detectable. [Aus der Bernstein-Forschung. Naturwissenschaften *59*, 294—298 (1972); 40 references]

[Rd 593 IE—M]

Methods for the analysis of narcotic analgesics and amphetamines are summarized by *S. J. Mulé*, particular interest being attached to the identification of these drugs after their isolation from biological material. Separation from the biological matrix is usually carried out by production of the free base and its extraction from the aqueous phase or by extraction from an Amberlite-XAD-2 column. Color reactions, like microcrystalline determinations and UV spectrometry, are not specific and sensitive enough for the identification of drugs, since in all cases extensive purification of the extract obtained from the biological material must be resorted to. Gas chromatography could very well be the most suitable method. It permits determination of drugs in the μg to ng range. Fluorescence spectroscopy appears to be very promising for the future, since it combines sensitivity and specificity with low time requirements. [Methods for the Analysis of Narcotic Analgesics and Amphetamines. J. Chromatogr. Sci. *10*, 275—282 (1972); 84 references]

[Rd 592 IE—X]

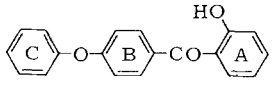
Patents

Abstracts of selected "Deutsche Offenlegungsschriften" (DOS), *i. e.* provisionally published specifications as filed with the German Patent Office

Porous, heat-cured resins with low densities are produced by formation and subsequent hardening of a water-in-resin emulsion, whose resin phase consists of an unsaturated polyester resin and/or a vinyl ester resin and monomers that can be copolymerized with these resins. A polyalkylene oxide block copolymer with a hydrophobic component having a molecular weight of at least 1000 is added to the emulsion as a nonionic surface active agent. Because of this addition, the cured resin emulsion gives off water even at room temperature, and can be readily dehydrated without the formation of cracks or fissures or other damage in the porous mass. The heat-cured resin can be worked *e.g.* like wood. It can be sawn, drilled, nailed, and screwed. [DOS 2046575; Dow Chemical Co., Midland, Mich.]

[PR 40 IE—E]

The novel use and production of 2-hydroxy-4'-phenoxybenzophenones *(1)* as stabilizers for organic material such as polyvinyl chloride, polyethylene, and polypropylene against the action of O_2, heat, and light is claimed. The benzene nucleus A may be substituted with CH_3, and nuclei B and



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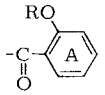


(2)

C may be substituted by halogen or substituted alkyl or alkoxy residues. The compound *(1)* is prepared by a Friedel-Crafts reaction of a diphenyl ether with a compound containing the residue *(2)* at $\leq 50\,^{\circ}C$. In the second step, R (lower alkyl) can be replaced by H by heating (acid hydrolysis with HBr). The new compounds may be incorporated into light-sensitive substances or applied as a protective layer. [DOS 2142353; Sandoz AG, Basel].

[PR 47 IE—B]

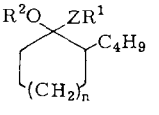
Scrap from polyoxymethylene plastics may be used as a source of formaldehyde in the production of reaction products of formaldehyde with aliphatic hydroxy compounds. The reaction proceeds in the presence of an aqueous acidic catalyst between 60 and 150 °C. Low molecular weight alcohols and diols or dihydrates of aldehydes are particularly suitable for use as hydroxy compounds. Examples of suitable catalysts are sulfuric acid, perchloric acid, phosphoric acid, and potassium hydrogen sulfate. The process is suitable for the production of formals and particularly of cyclic formals such as 1,3-dioxolane and 1,3,5-trioxolane. [DOS 2064100; Badische Anilin- & Soda-Fabrik AG, Ludwigshafen]

[PR 56 IE—I]

Flame-resistant plasticized polyvinyl chloride is obtained by the addition of the plasticizer tribromophenyl 2,3-dibromopropyl ether. The incombustibility of raw polyvinyl chloride, which is a valuable property, is greatly reduced by the usual additives, particularly plasticizers. The plasticizer mentioned, on the other hand, acts as a flameproofing agent without limiting the cold strength of the plasticized PVC mix or necessitating additional synergists such as antimony compounds. [DOS 2049188; Chemische Fabrik Kalk, Köln]

[PR 73 IE—T]

New carbocyclic perfumes *(1)* and their production are claimed.



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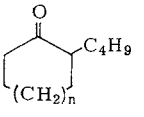


(2)

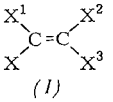
(3)

R^1 = H, methyl; R^2 = H, lower alkanoyl;
Z = $-C\equiv C-$, $-CH=CH-$, $-CH_2-CH_2-$;
n = 0,1,2; M = alkali metal, MgHal

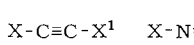
They are prepared by reaction of compounds *(2)* with an organometallic compound *(3)*. The hydroxyl group of the reaction product may be alkanoylated, and a triple or double bond may be hydrogenated to a double or single bond. [DOS 2155671; L. Givaudan & Cie. S.A., Vernier-Genève]

[PR 53 IE—D]

Modified olefin and diolefin homopolymers and copolymers containing polar groups, which exhibit very good technical properties, are produced by reaction of the polymers, *e.g.* 1,4-*cis*-polyisoprene, with an unsaturated compound of the type *(1)*, *(2)*, or *(3)* between 40 and 200 °C in the



(1)



(2) *(3)*

X to X^3 = H, COOH, COOR, CN, CHO, $CONH_2$, SO_3H, CH_2Cl; at least one of the residues X to X^3 is not H; the *cis* substituents of the C=C double bond may be bivalent residues, which react with ring formation;
R = alkyl, aryl

presence of free-radical catalysts, *e.g.* azodiisobutyronitrile, antioxidants, and aliphatic or cycloaliphatic hydrocarbons and/or ketones containing at least 5 C atoms, *e.g. n*-heptane and cyclohexanone, as a solvent.

Examples of suitable unsaturated compounds are allyl chloride, acrolein, acrylic acid, acrylonitrile, tetracyanoethylene, azodicarboxamide, and particularly maleic anhydride. The products can be made into curable objects having good green strength. [DOS 2143804; Snam Progetti S.p.A., Milan]

[PR 30 IE—C]

Deuterated, saturated, acyclic C_4—C_8 hydrocarbons containing functional groups (ethers, alcohols, monocarboxylic, dicarboxylic, or polycarboxylic acids or their ester or amide derivatives) and having boiling points of at least 100 °C for the liquids are prepared as follows: Saturated or unsaturated hydrocarbons containing one or more functional groups are brought into contact in the liquid state with deuterium gas in the presence of a metal catalyst of Group VII or VIII until the desired fraction of the hydrogen atoms has been replaced by deuterium atoms. The catalyst is advantageously held on a support, and the reaction temperature is up to about 300 °C. The compounds are used in research work, as high-temperature solvents, as lubricating oils, or as base fluids for lubricating greases. [DOS 2162535; Merck Sharp & Dohme (I.A.) Corp., New York]

[PR 54 IE—I]

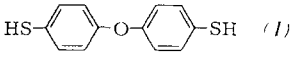
Cyanuryl chloride can be prepared by catalytic trimerization of cyanogen chloride in the gas phase with an aluminum silicate catalyst $Na_2O \cdot Al_2O_3 \cdot nSiO_2$ having pore sizes of about 6 to 15 Å and a molar ratio of silicon dioxide to aluminum oxide of at least 2.2 : 1 in the original and/or modified ion-charged form after treatment at a high temperature, preferably between 550 and 570 °C. The catalyst may also be subjected to carbon deposition; it can be used in a fixed bed or in a fluidized bed. [DOS 2159040; VEB Chemiekombinat Bitterfeld, Bitterfeld]

[PR 57 IE—I]

A new, greatly weakened living vaccine for rubella can be obtained by further growth of the rubella virus over at least ten passages in a tissue culture containing primary kidney cells of the guinea pig. The vaccine can be used for vaccination against German measles, and does not lead to the side effects observed in the past, even in adults. [DOS 2132911; Takeda Chemical Industries Ltd., Osaka]

[PR 90 IE—N]

4,4'-Dimercaptodiphenyl ether *(1)* can be used as a vulcanizing agent for natural and synthetic rubbers. This compound is obtained by reduction of diphenyl ether 4,4'-bis(sulfonyl chloride) with Zn/conc.HCl. The quantity of *(1)* required for vulcanization is not critical; it is preferably 1.5 to 4 parts by weight per 100 parts by weight of rubber. It is generally also necessary to add sulfur in a proportion of 0.05 to 0.5 part by weight as an activator. The types of rubber that can be vulcanized with *(1)* include all those that can be vulcanized in the usual manner as well as polychloroprene and silicone rubbers. [DOS 1643556; Uniroyal, Inc., New York]



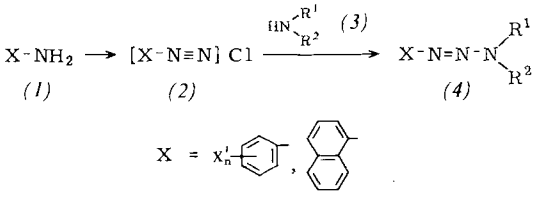
(1)

[PR 38 IE—E]

Readily biodegradable carboxylated polyalkenes, which are very desirable from the standpoint of protection of the environment, are obtained by irradiation of a monomeric or polymeric hydrocarbon, *e.g.* polyethylene, polypropylene, or polybutadiene, in CO_2 under pressure. Ionizing radiation such as γ-radiation, X-rays, or high-energy electrons from any source may be used. The physical properties of the material, which is used *e.g.* as a packaging film or as fibers, are largely unaffected. Carboxylated polyalkene fibers having a sufficiently high degree of carboxylation can also be readily dyed. [DOS 2148927; Standard Research Institute, Menlo Park, Calif.]

[PR 72 IE—T]

Viricidal, insecticidal, and miticidal agents contain triazene derivatives *(4)* as active ingredients. The agents are not phytotoxic, and can be used in agriculture and horticulture to combat several types of viruses that attack useful and ornamental plants (such as rice, grain, vegetables, potatoes, fruit, and flowers). The agents can also be used against harmful insects and against red spider. The triazene compounds *(4)* can be prepared by diazotization of an aromatic amine *(1)* and reaction of the diazonium chloride *(2)* with an aliphatic or cyclic amine *(3)*.



X' = H, CH_3, OCH_3, Cl; n = 1, 2; R^1, R^2 = —CH_2—CH=CH_2, lower alkyl; $R^1 + R^2$ = (CH_3-substituted) heterocyclic group (C_4—C_6) containing N

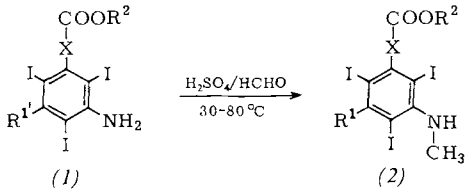
[DOS 2147259; Farbenfabriken Bayer AG, Leverkusen]

[PR 87 IE—N]

Living polymers are obtained by addition of a monomer having the general formula H_2C=CXX' (where X is hydrogen or an organic substituent and X' is an organic substituent, and the sum of the Hammett substituent constants of X and X' lies in the range between −0.2 and 0.1) to a mixture of alkali metals having a large surface at a temperature in the range between −100 and 30 °C in an inert atmosphere. Aromatic hydrocarbons, for example, are added as activators in a stoichiometric excess to the alkali metal and a Lewis base. [DOS 1595048; Nippon Soda K.K., Tokyo]

[PR 83 IE—E]

Monomethylaminotriiodophenyl compounds *(2)* or their salts with physiologically acceptable bases are valuable X-ray contrast media and are characterized by favorable elimination *via* the bile and by a low toxicity. The compounds can also be converted by *N*-acylation into known X-ray contrast media, *e.g.* metrizoic acid. The compounds are prepared by reaction of the amines *(1)* with a mixture



R^1, $R^{1'}$ = *e.g.* H, I, (cyclic) acylamino; R^2 = *e.g.* H, lower alkyl; X = *e.g.* —CO—N(C_6H_5)-alkylene, single bond

of concentrated sulfuric acid and (excess) formaldehyde. [DOS 2050217; Schering AG, Berlin and Bergkamen]

[PR 88 IE—N]

In a new process for the production of chloropyridines, in which there is no need to start with a preformed pyridine ring, cheap ε-caprolactam or cyclohexanone oxime is allowed to react with chlorine in the vapor phase at a temperature of least 250°C (400 to 600°C). The chlorine and the caprolactam or cyclohexanone oxime are preferably preheated separately. The starting materials may be diluted with inorganic diluents (N_2 or steam) or with organic diluents that are inert to chlorine (CCl_4). The new method is particularly suitable for the preparation of pentachloropyridine, but chloropyridines having less than five chlorine atoms can also be obtained, the proportion of these products depending on the quantity of chlorine, the reaction temperature, and the residence time. In general, at least 5 mol of chlorine should be used per mol of caprolactam or cyclohexanone oxime. If pentachloropyridine is desired as the main product, 15—30 mol of chlorine are used per mole of starting material. The preferred residence times for the mixture in the reaction zone are between 10 and 30 seconds. In one example, ε-caprolactam is allowed to react with 18 mol of chlorine per mol of caprolactam at 530°C, with a residence time of 20 seconds. In addition to 2,3,4,6- and 2,3,5,6-tetrachloropyridines, the product contains pentachloropyridine in a yield of 86%. [DOS 2141632; Imperial Chemical Industries Ltd., London]

[PR 75 IE—U]

Hydrogenation catalysts for the hydrogenation of polymers in viscous solution at low temperatures and low hydrogen pressures consist of a reaction product of at least one metal chelate of the metals nickel, cobalt, and iron, the chelating agent being bonded to the metal *via* a nitrogen atom and an oxygen atom, with at least one reducing agent having the formula MR_n, where M is lithium, magnesium, or aluminum, R is a hydrocarbon or alkoxy group containing 1 to 12 carbon atoms or hydrogen, and *n* is the valency of M. The catalyst can be obtained by dissolution or dispersion of the metal chelate in an inert solvent and reaction with the reducing agent; however, the catalytic components may also be mixed with the polymer solution to be hydrogenated. The catalyst is used for the hydrogenation of polymers that contain C=C double bonds, C≡C triple bonds, and C≡N triple bonds. [DOS 1767832; Bridgestone Tire Co. Ltd., Tokio]

[PR 37 IE—E]

BOOK REVIEWS

Aromaticity. By *P. J. Garratt.* McGraw-Hill Book Co., London 1971, 1st. Edit., viii, 184 pp. numerous figures, bound £ 3.40.

In the course of a century the concept of aromaticity has greatly promoted the synthetic and theoretical development of organic chemistry. This process is described in the present work, which is intended as a textbook. It first explains in detail, by a discussion of the classic pair benzene and cyclooctatetraene, the physical and chemical differences between Hückel systems with closed and with open shells. This is followed by the treatment of annulenes, monocylic aromatic and antiaromatic ions, annulenones, and fulvenes. The other chapters are devoted to heterocycles, polycyclic compounds, homoaromatic π systems, and finally the aromatic transition states of pericyclic reactions.

A very large volume of material is presented within this broad framework, often with the welcome inclusion of spectroscopic, magnetic, kinetic, and structural data, and the field is covered in part up to 1971. In line with the textbook style, the references are mainly confined to lists of secondary literature at the ends of chapters. The consistent use of the Frost-Musulin formalism or the Dewar PMO method for the determination of delocalization energies is didactically commendable, as it makes these parameters, which are fundamental to the understanding of aromaticity, accessible even to students and chemists with no mathematical background. On the other hand, the treatment of aromatic transition states in four pages, where (incorrectly in this context) even homoaromatic ions are found as solvolysis intermediates, is simply too short. This chapter, which is certainly not out of place, should be rewritten and expanded in a new edition. The opportunity should then be taken to rid the book of errors.

The book is well written and abundantly provided with reaction schemes. It will provide advanced students and chemists specializing in other fields with a good survey of the field that has benefited from the concept of aromaticity. Moreover, it also represents a reasonably priced reference work for those who are already conversant with this field.

Wolfram Grimme [NB 1121E]

Carbene Chemistry. By *W. Kirmse.* Academic Press, New York—London 1971. 2nd Edit. xi, 615 pp., numerous figures and tables, bond $ 33.—.

One of the heuristic principles of the last few decades in organic chemistry (which is certainly not short of ideas) is the carbene concept, which was introduced in the early

1950's and rapidly blossomed into a classical field of research. *Kirmse's* book, which first appeared in 1964, provided a first comprehensive survey and soon became *the* book on this subject; it was also the prelude to a distinguished series of monographs on organic chemistry edited by *A. T. Blomquist* (now with *H. Wasserman)*, which now comprises 23 volumes. The rapid further development of carbene chemistry, which is impressively reflected in the fact that the number of publications on the topic has now trebled, is undoubtedly a consequence not only of the many mechanistic problems and preparative possibilities but mainly (in the author's opinion, which is surely correct) of the emotional impact of the concept of bivalent carbon. The present second edition, though identical in its external presentation, is a completely rewritten book, with twice as many pages as the first edition, and with 2500 references extending up to 1970.

To allow a coherent presentation of the extensive material in its many aspects, *Kirmse* has (very skillfully in the reviewer's opinion) divided the book into two main parts; in the first part (entitled Methylene Transfer Reactions), consisting of the four chapters Introduction, Photochemical and Thermal Methylene Transfer Reactions, Organometallic Methylene Transfer Agents, and Base-Induced α-Eliminations, the emphasis is on the ways in which carbenes and carbenoids are formed, while the second part deals with their structure and reactivity and is divided into the following eight chapters: Structural Theory of Carbenes (written by *J. F. Harrison*), Spectra of the Carbenes, Reactions with C—H Bonds, Additions to Alkenes, Additions to Alkynes, Additions to Aromatic Compounds, Reactions Involving Hetero Atoms, and Rearrangements. Another chapter, which was written by *P. P. Gaspar* and *B. J. Herold*, deals with silicon, germanium, and tin structural analogs of carbenes (the authors offer didactic objections to the more usual term "carbene analogs").

The book is fluently, clearly, and concisely written. A number of omissions and instances of personal emphasis are hardly to be avoided in view of the abundance of material, and are of little consequence owing to the many references to original literature. The index and numerous cross references in the text enhance the value of the book as a reference work. All in all, the second edition will carry on the role of the first edition as an authoritative book on carbene chemistry, and is a must for any chemical library and for the bookshelves of any scientist who is interested in this subject.

Gert Köbrich [NB 103 IE]

Models in Chemical Science. An Introduction to General Chemistry. By *G. S. Hammond, J. Osteryoung, T. H. Crawford*, and *H. B. Gray*. W. A. Benjamin, Inc., New York, 1971, 1st Edit., xiii, 422 pp., numerous figures, bound *ca.* DM 38.—.

Teaching Guide for Models in Chemical Science. By *R. L. Keiter*. W. A. Benjamin Inc., Menlo Park, Calif. 1971. 1st Edit. x, 491 pp., bound.

Because of the curricula followed in many schools, the background knowledge of those embarking on a chemistry course often leaves much to be desired. An introduction to the basic principles of chemical thought, with a very limited range of subject matter, can be of great assistance in such cases. There is no shortage of textbooks of this type in English-speaking countries. However, these are often aimed at the American high-school level, and are too simple for German university entrants. The present book by *Hammond et al.* is an exception. The beginner is presented here with the essential ideas of chemistry, with a clarity that is often exemplary. The axiomatic nature of these ideas is never concealed. On the contrary, the fundamental aim of the authors is to demonstrate clearly the model character of all our chemical views. This is further emphasized by *Keiter's* excellent supplement, which is a valuable aid to tutors in the tutorial treatment of the material in the textbook.

More than half of the book is devoted to the development of the concept of chemical structure and bonding in molecules, liquids, and solids. It is a pity that the concept of symmetry, which is so important nowadays, is not introduced here.

A chapter on solutions, which provides the first contact with thermodynamic concepts, is followed by a detailed treatment of equilibrium in chemical reactions and a very brief chapter on the various reaction types. After a chapter on chemical kinetics the book ends with an example of chemical taxonomy from the field of carbon and silicon compounds.

A feature that the reviewers feel to be very valuable is the list of chemical concepts discussed, with dictionary-like definitions, after each chapter and at the end of the book.

Nowhere is it easier to find omissions than in an introduction to general chemistry. It is to the authors' credit, in our opinion, that they did not yield to the temptation to introduce more material at the expense of clarity and detail.

The treatment of the diversity and classification of chemical reactions is admittedly too short, but a course in chemistry is largely devoted to this topic in any case. This book is unmatched as an introduction to the main concepts of modern chemistry for course entrants. The text is excellently arranged, and is supported by clear diagrams that make a lasting impression.

Guido Hartmann and *Siegfried Hünig* [NB 113 IE]

The Alkaloids. Vol. 13, Chemistry and Physiology. Edited by *R. H. F. Manske*. Academic Press, New York—London 1971, 1st Edit., xv, 457 pp., numerous figures, bound $ 24.—.

In this new volume, the editor has again managed to find important specialists to write the nine chapters.

K. W. Bentley (283 references) has collected a large number of general and special reactions of morphinan derivatives. This contribution covers articles on mass-spectrometric fragmentations as well as the numerous synthesis, degradation, and rearrangement reactions. 26 new morphinan alkaloids are presented, substances having the hasubanonine skeleton also being listed here. *M. Shamma's* article on the small group of spirobenzylisoquinoline alkaloids (26 references) deals mainly with problems of their structural elucidation and synthesis. *A. Brossi, S. Teitel*, and *G. V. Perry* (97 references) present a concise survey of the principal chemical, biosynthetic, and pharmacological discoveries in the field of ipecacuanha alkaloids. The number of pages required has increased from 2 in Volume 7 to 20 in the present volume. *B. Robinson* reviews recent syntheses of the physostigmine skeleton and publications on the determination of the absolute configuration and the pharmacology of the Calabar bean alkaloids (28 references).

The elucidation of the complicated structures of the Galbulimima alkaloids is largely due to the authors of the 5th chapter, *E. Ritchie* and *W. C. Taylor*, who review the analytical works that have appeared since the publication of their last article in Volume 9 (1967). *R. S. Kapil* (44 references) outlines the publications since 1964 on a new subgroup of the indole alkaloids, *i.e.* the carbazole alkaloids. *M. Curcumelli-Rodostamo* correlates the 30 or so new bisbenzyltetrahydroisoquinolines isolated in the last four years (up to 1970) with the previously known compounds, and adds further important information (124 references). An abundance of recent syntheses, stereochemical investigations, and physiological and pharmacological findings explain the renewed discussion of the tropane alkaloids (*G. Fodor*, 194 references). The last chapter, "Alkaloids Unclassified and of Unknown Structure" (116 references), was written by *R. H. F. Manske*.

The favorable overall impression given by this alkaloid volume is only very slightly weakened by the few errors (mainly in the first chapter): pentavalent carbon (formula X), missing or incorrect reaction arrows (p. 155), a formula scheme under an incorrect heading (p. 155), and irregularities in the characterization of stereoisomerization and ^{14}C labeling (p. 374).

Spot checks show that the references are fairly free from errors (though one should read 1965 for 1925 in reference 3, p. 156). After reading this book, the reader will be in no doubt as to the unsuitability of Roman numerals for numbering chemical formulas. The very short subject index gives only a hint of the abundance of information presented.

All the articles show impressively the important part played by the proper use of modern physical methods in the successes that have been achieved. They also show how youthful alkaloid chemistry has remained, despite its long history.

The book can be unreservedly recommended to all chemists, botanists, and pharmacologists who are interested in the alkaloid field. It should certainly find a place in any library.

Volker Teetz [NB 117 IE]

Gel Permeation Chromatography. Edited by *K. H. Altgelt* and *L. Segal*. Marcel Dekker Inc., New York 1971, 1st Edit., xvii, 646 pp., numerous figures bond $ 24.75.

The book contains the lectures from a symposium on this topic held by the American Chemical Society at the beginning of 1970, which were published in 1970/71 in "Separation Science". The editors have tried to take account of the wide range covered by the fields of interest of the lecturers by division of the material into the following chapters: Fundamental Introduction; Survey of Theories and Evaluation Methods; New Developments; Application to Polymer and Petrochemical Problems. The specialist will find here a great deal of valuable advice for his own theoretical and experimental work, *e.g.* on the gel permeation chromatography (GPC) of high molecular weight polyethylene and polypropylene with an IR detector and with tetrachloroethylene as a solvent at high temperatures; on corrections required in the evaluation; on the use of the universal calibration after *H. Benoit*; on the GPC methods known up to 1970 for the investigation of copolymers.

From the title of the book, one would expect a substantially complete description of the GPC technique, the theories, and its uses; the book by *Determann* [Gelchromatographie (Gel Chromatography). Springer-Verlag, 1967] on general gel chromatography might serve as a pattern in this respect. A coherent and (to the chemist) more readily comprehensible introduction to the physical material would also be possible within this framework. However, the contributions presented are well able to widen and deepen the knowledge of those who are familiar with GPC.

Manfred Unbehend [NB 118 IE]

Spectroscopic Properties of Inorganic and Organometallic Compounds. Vol. 4. Specialist Periodical Reports. Published by The Chemical Society, London 1971, 1st Edit., xviii, 604 pp., numerous figures bound £ 10.00.

Volume 4 presents a survey of the literature published in 1970 in the following fields: nuclear magnetic resonance (185 pages); nuclear quadrupole resonance (10 pages); microwave spectroscopy (13 pages); vibrational spectra (260 pages); and Mössbauer spectroscopy (95 pages). The collection of literature is complete, and is presented in such a way that all the significant developments in these fields are specially picked out. Not only are the results reported, but possibilities for using spectroscopic information are also shown.

Each chapter is complete in itself, and provides an insight into the range of applications that have been found for the various methods. The books and reviews that have been published are discussed in the introduction to each chapter and the main subjects of the investigations are emphasized. Each chapter contains sections arranged according to the lements. This arrangement facilitates rapid scanning.

This volume can be warmly recommended to everyone concerned with these methods. The series is particularly valuable for those who wish to familiarize themselves with this field (degree and doctorate candidates). One obtains here a large, ordered literature survey in a very short time with a minimum of work.

H. W. Roesky [NB 122 IE]

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International Edition in English

Chemistry and Biosynthesis of the Hypothalamic Releasing and Inhibiting Neurohormones[**]

By Karl Folkers, Nils-Gunnar Johansson, Fred Hooper, Bruce Currie, Hans Sievertsson, Jaw-Kang Chang, and Cyril Y. Bowers[*]

The hypothalamus secretes hormones which in turn affect the release of hormones from the anterior lobe of the pituitary gland. Evidence has so far been adduced for the existence of seven hypothalamic releasing hormones and three inhibiting hormones. These neurohormones are all oligopeptides and occur in only nanogram amounts in the hypothalamus. The study of synthetic analogs has provided valuable information regarding their mechanism of action.

1. Summary

1.1. Background

The hypothalamus is a region of brain tissue which has significant functions in mammalian physiology and particularly influences the secretion of hormones of the anterior lobe of the pituitary gland. The tentative list of hypothalamic neurohormones consists of seven releasing hormones and three inhibiting hormones.

The thyrotropin releasing hormone (TRH) and the luteinizing hormone releasing hormone (LRH) have been isolated and structurally elucidated. TRH is a tripeptide, pGlu-His-Pro-NH_2, and LRH is a decapeptide, pGlu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH_2. TRH and LRH have been synthesized by various combinations of classical reactions and solid-phase procedures.

It has been commonly considered that there is a "unitary" hormone relationship between the hypothalamus and the pituitary, *i.e.*, one hypothalamic hormone regulates one pituitary hormone. However, this "unitary concept" may not be invariant.

LRH releases the luteinizing hormone (LH) and the follicle stimulating hormone (FSH), and has been designated as the gonadotrophin releasing hormone for both LH and FSH. TRH releases thyrotropin and prolactin; current investigations should reveal whether it is the intrinsic regulator of both these pituitary hormones.

A peptide isolated from the hypothalamus, Val-His-Leu-Ser-Ala-Glu-Glu-Lys-Glu-Ala, has been proposed as the growth hormone releasing hormone. However, its essential failure to release growth hormone by radioimmunoassay appears to invalidate this claim.

Two peptides displaying the activity of a melanocyte release inhibiting hormone have been isolated, *viz.* Pro-Leu-Gly-NH_2 and Pro-His-Phe-Arg-Gly-NH_2. Pro-Leu-Gly-NH_2 did not inhibit release of MSH in tests by other investiga-

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C. Y. Bowers
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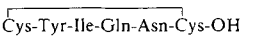
New Orleans, Louisiana 70112 (USA)

[**] Hypothalamic Hormones Part 42. This survey is an updated and expanded version of a presentation at the Quebec Conference and Exhibition in Canada on June 5, 1972 by *Karl Folkers*.

tors who concluded that the nature of MRIH is uncertain, but for the rat may be tocinoic acid



or a related peptide. Tocinoic acid does not inhibit the release of MSH in amphibian pituitary tissue. The pentapeptide H-Cys-Tyr-Ile-Gln-Asn-OH, on the other hand, does act as MSHRH.

According to data obtained with labeled amino acids, biosynthesis of TRH and LRH in systems from hypothalamic tissue appears to involve soluble enzymes and not DNA-dependent RNA-directed reactions.

The tetrapeptide pGlu-Tyr-Arg-Trp-NH_2 was the first synthetic peptide having LRH activity, which is remarkable since the positions of Tyr- and Trp- in this tetrapeptide differ from those in LRH. Both the π-electrons and the basicity of protonated His- of TRH may be functional for the release of TSH, release possibly resulting from both complexing and an ionic mechanism involving a negatively charged receptor site. The Arg^8- moiety of LRH is apparently important to hormonal activity and potency. The positive charge of protonated Arg- in LRH could play an ionic role in release comparable with that of protonated His- in TRH.

Differences in activities of analogs of TRH and LRH at dosages up to 100-fold that of the hormone may arise predominantly from the structures of the analogs. Differences in activities of analogs at dosages of 10000-fold and higher may be due to a combination of molecular variations of both the hormone and that of the receptor site.

Substance P has been characterized as Arg-Pro-Lys-Pro-Gln-Gln-Phe-Gly-Leu-Met-NH_2, and the partial structure of neurokinin is reported as pGlu-, 1 Lys-, 2 Arg-, 1 Asp-, 1 Glx-, 2 Pro-, 1 Ile-, 2 Leu-, 2 Tyr-. Although these two peptides have not been classified as hypothalamic neurohormones, they are derived from hypothalamic and other tissue of the mid-brain, and neurokinin has an initial pGlu- moiety. Substance P has sialogogic activity and neurokinin has hypotensive and other physiological activities.

New therapeutic advances can be anticipated from these new hypothalamic neurohormones.

1.2. Hypothalamus and Pituitary Gland

The hypothalamus is a small section of tissue of the diencephalon, the posterior part of the prosencephalon[1]. Apart from the hypothalamus, the prosencephalon consists of the thalamus, metathalamus, and epithalamus. The hypothalamus is not considered as an organ with boundaries, but rather as a region of brain tissue which has significant functions in many aspects of mammalian physiology.

This tissue is apparently responsible for hormonal regulation of many basic functions of life and also affects behavior. While the hypothalamic region of the brain is only a part of a complex anatomical system, the functions of this region are so strategic that derangement can have profound effects. The hypothalamus must be regarded as part of the series of complex neural systems involving the brain stem, cerebral hemispheres, and other parts of the diencephalon. The hypothalamus is presumably influenced by the great sensory systems of the brain including thalamic and cortical influences for behavioral and autonomic expressions.

The hypothalamus and the pituitary gland are separated by a further region of tissue (median eminence)[1].

The hypothalamus influences the secretory activities of the anterior lobe of the pituitary gland. This hypothalamus-pituitary relationship influences the thyroid gland, adrenal gland, testis, ovary, bone, *etc.*

The hypothalamus and the pituitary interact *via* neural secretions or neurohormones. Fibers of hypothalamic origin, which are estimated to number 100000 in man, terminate in the posterior lobe of the pituitary where they release the nonapeptides vasopressin and oxytocin. Other fibers of hypothalamic origin terminate in the median eminence close to capillaries that are connected to the portal blood vessels of the anterior lobe of the pituitary. The blood flowing through this system transports the releasing and inhibiting hormones discussed in this report.

To summarize, the nonapeptides vasopressin and oxytocin are neurohormones which are released by nerve cells and function in the posterior lobe of the pituitary. The releasing and inhibiting hormones are transported by a network of capillaries and act upon the anterior lobe. Vasopressin, oxytocin, thyrotropin releasing hormone, and luteinizing hormone releasing hormone are peptides of relatively low molecular weight, *i.e.* containing nine, nine, three, and ten amino acids, respectively.

2. Hypothalamic Releasing and Inhibiting Neurohormones

The hypothalamic neurohormones which act upon the anterior pituitary were postulated by *Hinsey*[2] and by *Green* and *Harris*[3] and were studied by many other investigators between 1937 and 1949. During the following 20 years or so, seven hypothalamic hormones were proposed on the basis of biological data concerning the release of corresponding anterior hormones. Three additional hypothalamic factors or hormones were also proposed which appear to inhibit the release of their corresponding hormones from the anterior pituitary. For many years it was commonly thought that one hypothalamic hormone controls one hormone of the anterior pituitary; recently, this "unitary concept" may have been breached since a single hypothalamic hormone appears to release the two pituitary hormones LH and FSH and another one seems to release both TSH and PRL. However, the evidence proving the two dual releases may yet be incomplete, and the "unitary concept" is not necessarily excluded.

The neurohormones of the hypothalamus have been designated as factors, but since their chemistry and biology comply with the definition of a hormone, the early nomen-

Table 1. Tentative list of hypothalamic releasing and inhibiting hormones (see text for relevant literature).

Releasing hormones Name	Abbreviation
1. Thyrotropin releasing hormone	TRH, TRF
2. Luteinizing hormone releasing hormone	LRH, LHRH, LRF
3. Follicle stimulating hormone releasing hormone	FRH, FSHRH, FRF
4. Corticotropin releasing hormone	CRH, CRF
5. Growth hormone releasing hormone	GRH, GHRH, GRF
6. Prolactin releasing hormone	PRH, PRF
7. Melanocyte stimulating hormone releasing hormone	MRH, MSHRH, MRF
Inhibiting factors or hormones	**Abbreviation**
1. Growth hormone inhibitory factor	GIF
2. Prolactin inhibitory factor	PIF
3. Melanocyte inhibitory factor	MRIF, MIF, MRIH

clature should be updated and the designation "hormone" adopted.

Table 1 lists the seven proposed releasing hormones, as studied by many investigators. This particular list is based on the concept of one hypothalamic hormone releasing one pituitary hormone. One can anticipate that further hypothalamic hormones may be added as they become biologically characterized. The three hypothalamic inhibiting hormones are also listed in Table 1, again assuming one hypothalamic inhibiting hormone for one hormone of the anterior pituitary.

2.1. Hypothalamic Releasing Hormones of Established Chemistry

2.1.1. Isolation

The isolation of even the first of these hypothalamic releasing hormones in pure form involved many years of effort. At least two major sources of difficulty were encountered. Only nanogram quantities of the releasing hormones appear to be present in the hypothalamic tissue of a single animal, and the hypothalamic fragment of one pig weighs at most 500 mg. Consequently, hundreds of thousands of the correct and minute pieces of tissue had to be knowingly removed from equivalent numbers of pigs, sheep, or other farm animals at slaughter houses. The isolation of milligram quantities of a pure hormone required for structural elucidation from these hundreds of thousands of hypothalami was a tedious task.

Associated with this difficulty of isolation were the problems of *in vivo* and/or *in vitro* assays for biological monitoring of the chemical isolations. These assays had to be devised and improved; they were frequently complicated and sometimes of questionable significance and even of doubtful specificity. It had been correctly predicted that the first hypothalamic releasing hormone to be chemically elucidated would be the thyrotropin releasing hormone (TRH) because a good assay had been evolved from the studies of many investigators which could guide the isolation of this particular hormone.

The final isolation of the porcine thyrotropin releasing hormone was reported by *Schally et al.*[4], and that of the corresponding ovine hormone by *Burgus* and *Guillemin*[5]. Porcine luteinizing hormone releasing hormone was isolated by *Schally et al.*[6], and ovine LRH by *Amoss et al.*[7].

Present knowledge of the organic chemistry of two hypothalamic releasing hormones should facilitate the continuing chemical and biological research directed toward the elucidation of other hypothalamic hormones, not only in the planning stage, but also in the laboratory. While the multiple chemical steps and countless biological assays required to obtain additional hormones may be somewhat less laborious than for TRH and LRH, it is still evident that the isolation of these additional hormones will involve truly prodigious efforts and many potential pitfalls. Also, the budgets required to sustain such efforts represent a financial problem.

2.1.2. Chemical Structure

The chemical structures of the two hypothalamic releasing hormones established so far are shown in Figure 1. The thyrotropin releasing hormone (TRH) is a tripeptide. TRH releases thyrotropin from the anterior pituitary which in turn acts on the thyroid gland. TRH was later discovered to release prolactin (see Section 4). The second hypothalamic releasing hormone to be characterized is the luteinizing releasing hormone (LRH or LHRH).

Interestingly, one hypothalamic releasing hormone is a tripeptide and another a decapeptide, and both have a

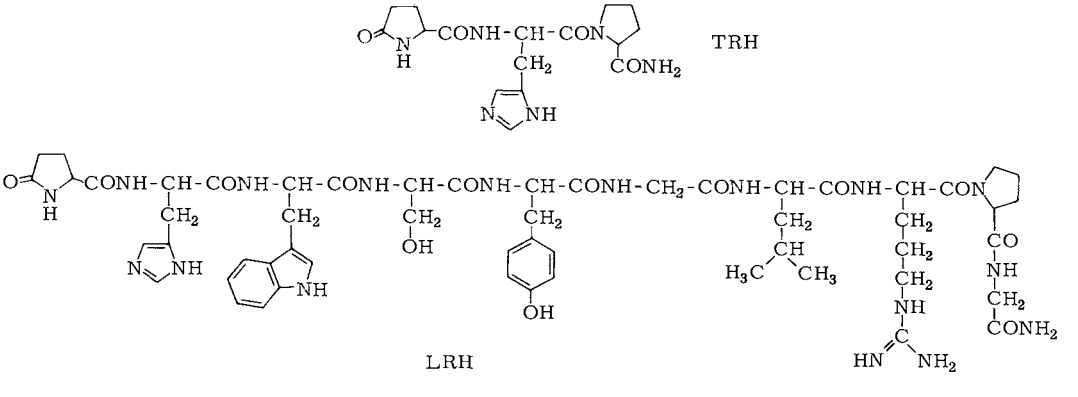


Fig. 1. Hypothalamic releasing hormones having established structures. Above: Thyrotropin releasing hormone (TRH), pGlu-His-Pro-NH_2. Below: Luteinizing hormone releasing hormone (LRH), pGlu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH_2.

pGlu- moiety at the N-terminus. No species specificity has yet been reported for either TRH or LRH. The discovery that a releasing hormone such as TRH could have the structure of only a "simple" tripeptide initially seemed hardly credible. When the next releasing hormone, LRH, was proposed to have the structure of a nonapeptide and then of a decapeptide renewed unbelief was aroused—such has been the challenge and excitement in this field. Possibly, new surprises are in store for future research into the remaining hypothalamic hormones.

The structures of TRH and LRH in Figure 1 have been emphasized as established. This situation contrasts with that in Figure 2 where structures are proposed for a hypothalamic inhibitory hormone and a releasing hormone; some of the data on the chemistry and hormonal activities are ambiguous, and certain artifacts appear to have been possible.

2.2. Proposed Structure of an Inhibitory Hormone

A proposed structure of melanocyte release inhibitory hormone (MRIH) is reproduced in Figure 2.

2.3. Proposed Structure of a Growth Hormone Releasing Hormone

Figure 2 also shows a structure proposed for the hypothalamic growth hormone releasing hormone (GHRH).

Whereas the structures of TRH and LRH are certain, those proposed for MRIH and GHRH apparently have not been confirmed. In the case of MRIH and GHRH, it is implied that although certain data may be correct, the identification of the MRIH is not clear, and the decapeptide proposed for GHRH is possibly an artifact, at least on the basis of published evidence. These statements are made in an effort to be both fair and objective in appraising the available information on MRIH and GHRH.

2.4. Chemical Structure of the Established Thyrotropin Releasing Hormone

It is now appropriate to survey in more detail the structures established for TRH and LRH and those proposed for MRIH and the GHRH. However, neither the step-by-step structure determination of TRH and LRH nor the protecting groups used in their syntheses will be considered in detail. Instead an overview is provided of the chemistry of these four hormones as known at this time.

The structure of the thyrotropin releasing hormone from both porcine[8,9] and ovine tissue[11] was established as that of pyroglutamyl-histidyl-prolinamide. It appears that

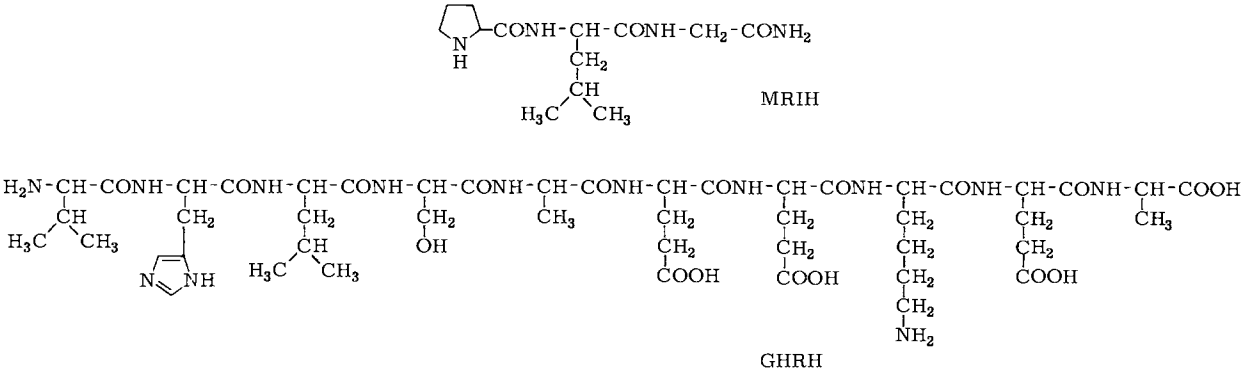
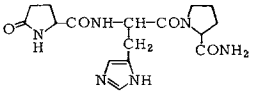


Fig. 2. Proposed structures for two hypothalamic hormones. Above: Melanocyte release inhibitory hormone (MRIH), Pro-Leu-Gly-NH_2. Below: Growth hormone releasing hormone (GHRH), Val-His-Leu-Ser-Ala-Glu-Glu-Lys-Glu-Ala.

this hormone has the same structure in other mammalian species, including man.

The synthesis of TRH was uniquely and unexpectedly achieved as a part of the structural study of porcine TRH in 1969[8,9], and it was concomitantly found that the biological properties of the porcine hormone and the synthetic pGlu-His-Pro-NH_2 are identical[10]. Syntheses of TRH

Table 2. Chemistry of the established hypothalamic thyrotropin releasing hormone.

Structure of TRH:	*Investigators*
	hormone from porcine tissue [8] *Folkers, Enzmann, Bøler, Bowers,* and *Schally* (1969) [9] *Bøler, Enzmann, Folkers, Bowers,* and *Schally* (1969) hormone from ovine tissue [11] *Burgus, Dunn, Desiderio,* and *Guillemin* (1969)
Synthesis: by various routes: with unprotected and protected amino acids and by the solid-phase procedure	[8] *Folkers, Enzmann, Bøler, Bowers,* and *Schally* (1969) [9] *Bøler, Enzmann, Folkers, Bowers,* and *Schally* (1969) [12] *Gillesen, Felix, Lergier,* and *Studer* (1970) [13] Flouret (1970) [14] *Rivaille* and *Milhaud* (1971) [15] *Chang, Sievertsson, Bogentoft, Currie, Folkers,* and *Daves* (1971)

by various routes, and with unprotected and protected amino acids in classical reactions, and by the solid-phase procedure of *Merrifield*, were achieved over the period of 1969—1971 by six groups of investigators. The six relevant publications[8,9,12–15][*] include the pioneering syntheses with the closely following and related synthetic studies (see Table 2).

2.5. Chemical Structure of the Established Luteinizing Releasing Hormone

The decapeptide shown in Figure 1 was provisionally proposed as the structure of LRH by *Matsuo et al.*[16] in 1971. This structure was based on data from a micro-scale degradation by a combined Edman-dansyl procedure, and a selective tritiation method for C-terminal analysis. The degradations were carried out directly on the digestion products of the hormone with chymotrypsin and thermolysin without separation of the fragments. Their proposed structure is correct, and they subsequently confirmed the structure by another sequence of degradation reactions[17]. It appears that *Matsuo et al.*[16] established this structure with 100 to 200 µg of the hormone isolated from porcine tissue.

Matsuo et al.[16] first published their proposed amino acid sequence for LRH with the comment that the evidence for the linkage pGlu-His- "is not very strong" and that "the mode of blocking at C-terminal Gly- still remains to be solved". It is nevertheless evident that their proposal of a decapeptide with "N-pGlu-" and a C-amide terminus was indeed reasonable, and provided a basis for synthesis of this decapeptide so that the synthetic peptide could be compared with the isolated hormone from porcine tissue and tested in the various bioassay systems for the appropriate hormonal activities.

Ovine LRH was isolated by *Amoss et al.*[7]. The primary structure, established by *Burgus et al.*[18,19], was reported in 1971–1972 to be identical to the decapeptide which had been previously established as the structure of porcine LRH. *Burgus et al.*[19] had at their disposal about 40 µg of the ovine hormone which represented about one-half of the total material derived from side fractions reserved from the early stages of the isolation of TRH. Altogether, their isolation of ovine TRH and LRH was said to utilize about 300000 sheep hypothalamic fragments.

2.6. Syntheses of Luteinizing Releasing Hormone

LRH has been synthesized by classical reactions, by the Merrifield procedure, and by combinations of classical and solid-phase techniques. The thirteen relevant publications[20–32] describe syntheses of pGlu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH_2 (cf. Fig. 1). There was essential agreement concerning the LH-releasing activity of the synthetic decapeptide.

Matsuo, Arimura, Nair, and *Schally*[24] reported that their synthetic decapeptide showed the same physico-chemical and biological properties as their isolated natural porcine hormone.

Many workers in the pharmaceutical industry have now synthesized LRH. For example, *Immer, Nelson,* and *Gotz* of Ayerst Laboratories in Montreal have announced their use of synthetic LRH in studies of animal and human fertility control.

2.7. Proposed Chemistry of Melanocyte Release Inhibiting Hormone

Kastin et al.[33] reported in 1968 on the extrapigmentary effects of the melanocyte-stimulating hormone in amenorrhoeic women. A highly purified preparation of MSH was administered to six women with secondary amenorrhoea. There was menstrual bleeding which might have represented a "rebound effect". The administration of MSH may have directly resulted in stimulation of the ovary. There were statistically significant changes in the concentrations of several components of the serum. The melanocyte-stimulating hormone darkens the skin of amphibians and permits adaptation to environment. It was considered that during the course of evolution, this pituitary hormone may have acquired extrapigmentary functions in mammals.

Celis et al.[34,35] had proposed that the C-terminal fragment of oxytocin (see Fig. 3), Pro-Leu-Gly-NH_2 is the natural MSH-release-inhibiting hormone.

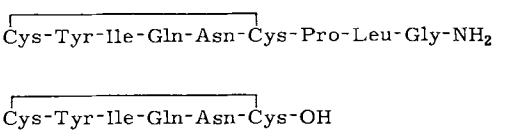


Fig. 3. Above: Oxytocin. Below: Tocinoic acid.

Nair et al.[36] isolated two MRIH-active peptides from bovine hypothalamic extracts, and found one of the peptides to show high MRIH activity and the other peptide to show much weaker activity. They determined the structure of the "main MRIH-active peptide" as Pro-Leu-Gly-NH_2, and synthesized this peptide. *Kastin et al.*[37] found that 10 ng of synthetic Pro-Leu-Gly-NH_2, when applied directly to the pituitary, resulted in lightening of the skin of a frog which had previously been darkened by the destruction of the hypothalamus. They recommended this modified assay for future studies with MRIH, because of its simplicity. The structure of the second MRIH peptide, with lower activity, was subsequently elucidated as H-Pro-His-Phe-Arg-Gly-NH_2[40].

A pentapeptide H-Cys-Tyr-Ile-Gln-Asn-OH was found by *Celis et al.*[38] to act like MSH-RH, because nanogram dosage of this peptide decreased the MSH content of the rat pituitary and increased the MSH concentration of plasma. This peptide also stimulated the release of MSH in animals with a lesion in the median eminence, which indicated a direct action of the peptide on the pituitary. Oxytocin has no effect on the MSH content of the pituitary.

Bower et al.[39] found that the synthetic tocinoic acid (see Fig. 3), which is the ring structure of oxytocin, inhibited

[*] Publications on tentative aspects of TRH structure and subsequent more detailed papers *etc.* will not be considered here.

the release of MSH from rat pituitaries *in vitro* at less than nanogram levels. However, this activity could not be demonstrated on the amphibian pituitary. In contrast to the report of *Kastin et al.*[37] Pro-Leu-Gly-NH_2 did not inhibit the release of MSH from either a rat or a frog system *in vitro*. *Bower et al.* believed that the differences could not be ascribed to differences in the techniques of assay. They concluded[39] that the exact nature of MRIH appears to be uncertain and suggested that, for the rat, tocinoic acid or a closely related structure may be a likely candidate as a natural MRIH.

2.8. Uncertain Chemistry of the Growth Hormone Releasing Hormone

Schally et al.[41] reported the isolation of the growth hormone releasing hormone (GHRH) from porcine hypothalami in 1969. The assay for GHRH activity was based on the depletion of the content of GH in the pituitary of rats and by other assays. In 1971, *Schally et al.*[42] reported the amino acid sequence of the isolated peptide to be Val-His-Leu-Ser-Ala-Glu-Glu-Lys-Glu-Ala, which is a decapeptide.

Veber et al.[43] observed a striking similarity between this decapeptide and a proposed amino-terminal sequence of the beta chain of porcine hemoglobin. Nevertheless, *Veber et al.*[43] synthesized the above decapeptide. *Schally et al.*[42,44] assayed the synthetic decapeptide and found that it stimulated the release of growth hormone, both *in vivo* and *in vitro*, by procedures in which the released growth hormone was measured by the tibia test method of *Greenspan et al.*[45] or by the assay for the sulfation factor. However, the synthetic decapeptide and the isolated peptide were essentially inactive in tests where the release of growth hormone was measured by a radioimmunoassay for rat growth hormone. It has not yet been reported whether mono-, di-, or tri-Gln- modifications of the decapeptide show GHRH activity on radioimmunoassay.

3. Biosynthesis of the Hypothalamic Hormones

In 1971 *Mitnick* and *Reichlin* reported[46] on the biosynthesis of the thyrotropin releasing hormone (TRH). They utilized hypothalamic fragments from the rat and examined the stalk median eminence and the ventral and dorsal sections. Labeled amino acids were added to the incubation system and after purification with the aid of carrier TRH and ^{125}I-TRH, labeled TRH was apparently obtained. However, no bioassays were reported.

From their results they deduced that only Glu-, His-, and Pro- were incorporated. Glu- is cyclized to give the pGlu- moiety and Pro- becomes Pro-NH_2 during the biosynthesis. It appeared that the biosynthetic mechanism involved soluble enzymes and not DNA-dependent RNA-directed reactions.

Johansson, *Hooper*, *Sievertsson*, *Currie*, and *Folkers*[47] at the University of Texas, in collaboration with *Cyril Bowers* of Tulane University, are also studying the mechanism of biosynthesis of the hypothalamic releasing hormones. We have utilized slices of porcine tissue and have added ^{14}C-Glu- to the incubation system. After several steps of purification and the utilization of synthetic LRH as carrier, it was concluded that labeled LRH had been biosynthesized. This conclusion is based on the observation that the LRH-Pauly spot was associated with radioactivity, and that hydrolysis of the radioactive spot yielded ^{14}C-Glu-. The radioactive spot was biologically active for the release of LH in the rat. It seems likely that the biosynthesis of LRH is by soluble enzymes, as reported for the biosynthesis of TRH by *Mitnick* and *Reichlin*.

4. The "Unitary Concept"

Early in this survey, reference was made to the "unitary concept" which has been based on the general idea that one hypothalamic releasing hormone controls one hormone of the anterior pituitary gland, and it was indicated that this "unitary concept" may have been breached. During the tedious and lengthy isolation of the luteinizing releasing hormone from porcine tissue, it was continuously observed that the releasing activities for both LH and FSH did not separate during the fractionations. Finally, *Schally et al.*[48] reported the isolation of LRH in an apparently homogeneous state, and stated that the hormone also has FSH releasing activity. The statement was based on the observation that partition chromatography in ten different solvent systems did not separate FSHRH activity from LHRH. The isolated hormone stimulated the release of both FSH and LH, *in vivo* as well as *in vitro*.

Subsequently, *Schally et al.*[49] were apparently convinced that the decapeptide intrinsically regulates the secretion of both luteinizing and follicle stimulating hormones, and they designated it as the "gonadotrophin-releasing hormone". It appeared to them that the overall control of FSH and LH secretion and the preferential release of one or the other of these gonadotrophins may be mediated by interactions between the decapeptide and steroids.

Additional information on the release of two pituitary hormones by one synthetic hypothalamic hormone has come from studies by *Bowers et al.*[50] who showed that synthetic pGlu-His-Pro-NH_2 (TRH) releases not only thyrotropin in man but also prolactin at all dose levels which have been tested. In fact, injection of only 10 μg of the synthetic tripeptide in man increased the serum levels of both thyrotropin and prolactin. There was no consistent release of GH, LH, or FSH, but the release of prolactin was invariable. This dual release of thyrotropin and prolactin raised the question of whether this synthetic tripeptide hormone is also a "natural regulator" of prolactin in man. The question is still being experimentally studied.

5. Discovery of LRH-Activity of pGlu-Tyr-Arg-Trp-NH_2

Turning now to the subject of the luteinizing releasing hormone, we shall describe the discovery of the first synthe-

tic peptide having the biological activity of LRH. *Bogentoft et al.*[51] studied concentrates of bovine and porcine LRH by chemical and enzymatic inactivations coupled with bioassays. They reported evidence for the presence of arginine, tyrosine, and tryptophan. *Amoss et al.*[52] and *Currie et al.*[53] had previously reported LRH to have a blocked N-terminus in the form of a pGlu- moiety.

Chang et al.[54] synthesized the six tetrapeptides which are possible for pGlu-, Arg-, Trp-, and Tyr-, and *Bowers et al.*[55] found that only one of the six is biologically active. Dosage in the range of 50–200 μg of pGlu-Tyr-Arg-Trp-NH_2 released LH *in vivo* under the conditions for the assay of LRH. It was obvious that this tetrapeptide is not the naturally occurring luteinizing releasing hormone.

On the basis of this LRH-active tetrapeptide, it was possible for *Bogentoft et al.*[51], *Chang et al.*[54], and *Bowers et al.*[55], to predict that LRH is a decapeptide and not a nonapeptide according to reports by *Schally et al.*[48]. This prediction was correct.

Recently, *Guillemin et al.*[56] confirmed that at comparable dosage the tetrapeptide pGlu-Tyr-Arg-Trp-NH_2 and synthetic LRH exhibit the same LRH activity *in vivo* and *in vitro*. It was also observed that pGlu-Tyr-Arg-Trp-NH_2 releases FSH with the same potency ratio as synthetic LRH. They also reported *in vivo* assay data which demonstrated that with pGlu-Tyr-Arg-Trp-NH_2, as well as LRH, a significant release of LH may be effected without a corresponding significant release of FSH. *Bowers et al.*[55] reported LH release without FSH release with as little as 50 μg and up to 600 μg of the tetrapeptide. *Guillemin et al.*[56] reported that at a dose of 500 μg a significant release of LH occurs without a release of FSH, but FSH was released (95% confidence) at a dose of 4 mg. The significance of FSH release at a dosage of 4 mg for this tetrapeptide is not clear.

6. Conformation-Sequence-Activity Relationships and Mechanism of Activity

When the sequence of the luteinizing releasing hormone became known, it was evident that the position of Tyr- and Trp- in the tetrapeptide and in LRH are reversed. Consequently, the hormonal activity of pGlu-Tyr-Arg-Trp-NH_2 *in vivo* is of additional interest with regard to conformation-sequence-activity relationships.

Sievertsson et al.[57] have reported on the role of the histidine moiety in the structure of the thyrotropin releasing hormone. Towards this objective, they synthesized the four analogs of pGlu-His-Pro-NH_2 (TRH) listed in Table 3. pGlu-Phe-Pro-NH_2 is remarkably active for the release of thyrotropin in mice, as measured by the T_3 method. A dose of 100 ng of this analog released nearly as much thyrotropin as 9 ng of TRH. They considered that both the π-electrons and the basicity of protonated His- may be functional for release of thyrotropin in the hormonal mechanism. It also appeared that release may result from both complexing and an ionic mechanism involving a

Table 3. Role of the histidine moiety in thyrotropic releasing hormone. Assay of tripeptides by the T_3 method in mice for release of thyrotropin.

Tripeptide	Dose [ng]	Counts/min ^{125}I
pGlu-His-Pro-NH_2 (TRH)	9	5612
pGlu-Phe-Pro-NH_2	100	3534
pGlu-Trp-Pro-NH_2	50000	204
pGlu-Tyr-Pro-NH_2	50000	100
pGlu-Phe-3Hyp-NH_2	50000	8

negatively charged group in the receptor site. Further studies of TRH analogs have been summarized by *Bowers et al.*[58].

We are also studying the conformation-sequence-activity relationships of the luteinizing releasing hormone. An advantageous new synthesis of pGlu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH_2 was achieved by "classical reactions" by *Chang et al.*[30,31,59]. In principle, the 1—6 sequence, pGlu-His-Trp-Ser-Tyr-Gly-, and the 7—10 sequence, Leu-Arg-Pro-Gly-NH_2, were synthesized separately and then coupled to give the decapeptide. The synthesis employed appropriate protective groups, good yields, and helpful stepwise purifications.

Since the Arg^8- moiety of the decapeptide is presumably important to hormonal activity and potency, this new synthesis provided the flexibility needed to replace Arg^8- with other moieties in the relatively small 7—10 sequence.

Table 4. Activity of analogs of luteinizing hormone releasing hormone.

Compound	Rel. dose
pGlu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH_2 (LRH)	1
Lys^8-LRH	5 – 50
His^8-LRH	200
Nva^8-LRH	100 – 300
Des-Arg^8-LRH	2000

The data in Table 4[30,31,59] reveal that Lys^8-LRH is a relatively active peptide. The other peptides tested were far less active than LRH, but a valid release at the high dosage levels recorded in Table 4 was still observed.

A molecular model of a possible conformation of the decapeptide LRH reveals that the planar indole and benzenoid moieties of Trp- and Tyr- could be in approximately parallel positions, because of possible π-bond interactions. Such parallel planarity may bestow some structural specificity for hormonal activity upon this molecule. The guanidino moiety of arginine could be relatively extended and exposed in this conformation of the decapeptide. Because of the basicity and exposure of the guanidino moiety, the positive charge of protonated Arg- could participate in the mechanism of the releasing activity. This ionic role of Arg- may be comparable with that of His- in TRH.

Continuing their studies on analogs of the luteinizing releasing hormone with a view to elucidating the release mechanism, *Chang et al.*[60] described seven new analogs of LRH, which were synthesized and assayed. Five of these seven analogs are listed in Table 5. Des-Leu^7-LRH and Des-Leu^7-Arg^8-Pro^9-Gly^{10}-LRH were active at a high dosage range. Des-Leu^7-Arg^8-LRH and Des-Arg^8-Pro^9-Gly^{10}-LRH were inactive at such dosages. The 7—10

sequence, Leu-Arg-Pro-Gly-NH_2, of the decapeptide was interesting for bioassay, because it contains the unique Arg- moiety. However, this tetrapeptide proved to be inactive.

Table 5. Activity of analogs of luteinizing hormone releasing hormone.

Compound	Rel. dose
pGlu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH_2 (LRH)	1
Des-Leu^7-LRH	20000
Des-(Leu^7-Arg^8)-LRH	50000, inactive
Des-(Arg^8-Pro^9-Gly^{10})-LRH	20000, inactive
Des-(Leu^7-Arg^8-Pro^9-Gly^{10})-LRH	20000—40000
Leu-Arg-Pro-Gly-NH_2	20000, inactive

The bioassays of the synthetic analogs described in Tables 4 and 5 led to further considerations concerning the mechanism of hormone release. The proximity of the positive charge of protonated Arg- in LRH and a companion negative charge on the receptor site may be important for an ionic reaction proposed as part of the release mechanism. This proposal is supported by the low activity of Des-Leu^7-LRH which could have a positive charge too remote for a normal ionic reaction.

In contemplating the conformation-sequence-activity relationships of LRH and its analogs, *Chang et al.*[60] observed that a division of the analogs into two categories provides help in understanding the obviously complex and overlapping relationships. The first category could include analogs of LRH which show significant release of LH at dosages up to 100-fold that of LRH. In this first category, differences in activities may arise predominately from the structures of the analogs. The second category could comprise those analogs which show significant release of LH at dosages of about 10000-fold and higher than the reference dosage levels of LRH. In this second category, differences in activities may be due to a combination of molecular variations of both hormone and release site. These enormous differences in the range of valid hormonal activity are observable because of the extraordinary potency of the hypothalamic hormones at picogram and nanogram levels.

Vale et al.[61] and *Monahan et al.*[62] have described two analogs of LRH modified at the His^2-position which were tested for release of LH in cultures of dispersed rat anterior pituitary cells. The analog in which glycine was substituted for His^2-, *i. e.* Gly^2-LRH, behaved as a partial antagonist: less than 50% of LH was released at maximum concentrations of LRH. Des-His^2-LRH had no significant activity for release. When added to the culture cell system at molar ratios of 10^3—10^4 times that of LRH, Gly^2-LRH and Des-His^2-LRH decreased the amount of LH secreted in response to LRH.

7. Substance P and Neurokinin

S. E. Leeman reported in June, 1972, at the 55th Canadian Chemical Conference in Quebec city, on the chemistry of two peptides which may have some relationship to the hypothalamic releasing hormones. While these peptides are not now classified as hypothalamic releasing hormones, they are derived from hypothalamic tissue and other tissue of the mid-brain.

Leeman and *Hammerschlag*[63] detected the presence of a sialogogic peptide in extracts of bovine and rat hypothalami while studying the activity of CRF (corticotropin releasing factor) in these extracts. *Chang* and *Leeman*[64] isolated this peptide and showed the presence of 1 Lys-, 1 Arg-, 2 Glx-, 2 Pro-, 1 Gly-, 1 Leu-, 1 Met-, and 2 Phe-. The total number of amino acids in the peptide is eleven and the molecular weight is about 1340. During the studies, it became evident that the peptide and the previously described Substance P are identical. Substance P was first detected in 1931 by *von Euler* and *Gaddum*[65] and found to have many interesting biological properties[66], but prior to this report[64] had never been obtained in pure form. Through cooperative studies with *Niall*[67] the sequence of the peptide was determined as Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH_2.

A peptide having this sequence was then synthesized by *Tregear et al.*[68] and was found to possess all the chemical and biological properties of the native peptide. Approximately 100000 bovine hypothalamic fragments were used to ascertain the chemistry of this peptide. A radioimmunoassay for Substance P has now been developed. Using this method, the concentration of Substance P found in substantia nigra tissue of human brain is estimated as 500 ng/g.

In further observations of the pharmacological activities of bovine hypothalamic extracts, *Leeman* observed the presence of a peptide that produced a characteristic vasodilation of the exposed cutaneous regions of anesthetized rats within seconds following intravenous injection. *Carraway* and *Leeman*[69] isolated the peptide responsible and found its activity to be associated with a transient hypotension. This peptide has now been found to contain 13 amino acids consisting of: 1 Lys-, 2 Arg-, 1 Asx-, 2 Glx-, 2 Pro-, 1 Ile-, 2 Leu-, and 2 Tyr-.

Of potential relationship to the hypothalamic releasing hormones, the structural studies showed that this peptide has a pGlu-moiety as do the thyrotropin and luteinizing releasing hormones; its structure would then be: pGlu-, 1 Lys-, 2 Arg-, 1 Asp-, 1 Glx-, 2 Pro-, 1 Ile-, 2 Leu-, 2 Tyr-.

This substance was tentatively designated neurokinin as in addition to its hypotensive activity it causes contraction of guinea pig ileal tissue while producing relaxation of the rat duodenum. In large doses it causes rats to become cyanotic.

8. Outlook

The chemistry of the hypothalamic releasing and inhibiting hormones is now clearly established as a new area in the field of biologically active peptides and signals a new era in the physiology of neurohormones. The chemical aspects of this new field are already attracting broad attention on the part of organic chemists, medicinal chemists,

biochemists, and enzymologists. Corresponding therapeutic advances in medicine can be anticipated from these advances in basic science.

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Repair Processes on Deoxyribonucleic Acid

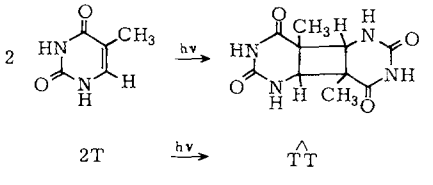
By J. Berndt[*]

Many cells have the ability to recognize and eliminate damage to their DNA, particularly thymine dimers formed by UV light. The elimination of this damage may be achieved by enzymatic, light-dependent cleavage of the dimers into the monomers (photoreactivation) or more frequently by dark repair, in which the damaged part is completely removed from the DNA. In this repair process, the DNA is incised by an endonuclease in the immediate vicinity of the thymine dimers. Oligonucleotides containing the thymine dimer are removed hydrolytically from the DNA by the 5→3′ exonuclease activity of DNA polymerase I (Kornberg enzyme). The resulting gaps are immediately closed by a *de novo* synthesis with the aid of the same DNA polymerase I, the complementary strand serving as a template (excision repair). The final step is the formation of the phosphodiester bond between the newly synthesized DNA fragment and the old DNA strand by a DNA ligase. Xeroderma pigmentosum patients lack the endonuclease as a result of a genetic defect; they therefore cannot eliminate thymine dimers from their DNA, and are extremely sensitive to sunlight. All information so far suggests that genetic recombination and DNA repair are performed by the same enzyme system.

1. Introduction

The genetic material of all cells consists of deoxyribonucleic acid (DNA). Two complementary DNA strands are held together by hydrogen bonds, and in this way they form a DNA double helix. The complementarity of the two strands is due to the fact that the adenine bases (A) of one strand form hydrogen bonds with the thymine bases (T) of the other, and hydrogen bonds are also formed between guanine (G) and cytosine (C). Until recently it was assumed that any modifications in the DNA due to external agents (UV light, X-rays, mutagens) must lead to the death of the cell, or in "favorable" cases to mutated daughter cells. Surprisingly, however, this is not the case, and many cells survive such harsh treatment. These cells possess a machinery by which damage to the DNA can be eliminated and the original form of the DNA double helix restored. This process is generally known as DNA repair.

Beukers and *Berends*[1] found that UV-irradiated, frozen thymine solutions contain dimers of thymine in which two thymine molecules are linked together by C—C bonds to form a cyclobutane ring. These dimers are relatively stable, and can be isolated *e.g.* by chromatography.



2T $\xrightarrow{h\nu}$ $\widehat{TT}$

The irradiation of DNA with UV light (260 nm) also leads to the formation of thymine dimers within a DNA strand at points where two thymine bases are neighbors in the same strand[2]. These dimers are the main reason for the biological action of UV light on the DNA[2,3]. They block DNA replication *in vitro*[4] and *in vivo*[5]; they are mainly responsible for the bactericidal action of UV light. The greater the number of thymine bases in the DNA of a bacterium, the more sensitive is this strain to the action of UV light.

In addition to the formation of thymine dimers in the DNA, UV irradiation can also lead to linkage of two cytosine molecules and/or a thymine and a cytosine mole-

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cule[6,7], though this happens to a smaller extent[*]. *Setlow* and *Carrier*[8] found the following (relative) quantities of dimers in *Escherichia coli (E. coli)*: $\widehat{TT}$ 50%, $\widehat{CT}$ 40%, $\widehat{CC}$ 10%. After exposure to high doses of radiation, the quantity of $\widehat{TT}$ is greater, especially when short wavelengths have been used. Dimerization of thymine molecules lying opposite each other in two neighboring DNA strands does not appear to occur[9].

As a result of DNA repair, therefore, thymine dimers and similar modifications are eliminated from the DNA. This can be achieved by two different mechanisms:

1. Photoreactivation

2. Dark repair.

These processes are discussed below.

2. DNA Repair

2.1. Photoreactivation

In 1949 *Kelner* observed that cultures of *Streptomyces griseus*[10], *Penicillium notatum*, and yeast cells[11] survived UV irradiation much better if they were subsequently exposed to visible light. This "photoreactivation" was then found to occur in a large number of microorganisms[12]. Light having a wavelength of 220—300 nm is most effective for the UV irradiation (dimer formation), whereas visible light having a wavelength of 310—440 nm is required for the photoreactivation process[13].

The first observation of an *in vitro* photoreactivation of UV-irradiated, purified DNA by an *E. coli* extract[14] was followed by similar investigations by *Rupert*[14-18] with yeast extracts. The results clearly showed for the first time that photoreactivation is an enzymatic process.

Yeast and *E. coli* extracts possessing photoreactivating activity have very similar spectra, with absorption maxima at 355 and 385 nm, but until recently it was not certain whether these are in fact the maxima of the "photon-absorbing unit" of the enzyme or of the enzyme-substrate complex[19]. A DNA-photoreactivating enzyme was recently purified seventy-thousand-fold from yeast and the properties of the enzyme were studied in detail[20]. The molecular weight was found to be 53000 and the enzyme had an excitation maximum at 385 nm and a fluorescence emission maximum at 485 nm. These two maxima correspond to the chromophoric groups of the enzyme, but these groups have not been characterized so far.

Obviously, the specificity of the enzyme for a cleavage of dimers is not very high, but the rate of cleavage is greatest for thymine dimers[13].

The photoreactivating enzyme acts by energy transfer, splitting the nucleotide dimers (particularly those of thymine) into monomers; normal adenine-thymine pairing is then again possible, and the function of the DNA is restored.

UV-damaged RNA is not attacked by the photoreactivating enzyme, but dimers of the single-stranded DNA of the phage ΦX174 can also be split into the monomers[13]. The double-stranded structure of the DNA thus does not seem to be a necessary condition for the activity of the enzyme.

The photoreactivation is found mainly in microorganisms, but is not restricted to this group of organisms. A similar photoreactivation has also been observed in mammalian cells[21-24], and photoreactivating activity was recently detected in tissue cultures from the (American) opossum and from the rat kangaroo[25]; however, the enzyme was not characterized further.

Since a much simpler enzyme assay is now available[25a], it should be possible to study the mechanism of the photoreactivating process in greater detail.

2.2. Dark Repair

A much more important repair process is that known as dark repair. This name does not mean that it occurs only in the dark, but simply that light plays no role in the process. This type of repair is capable of eliminating not only dimers of the pyrimidine derivatives, as in photoreactivation but also other types of damage to the DNA.

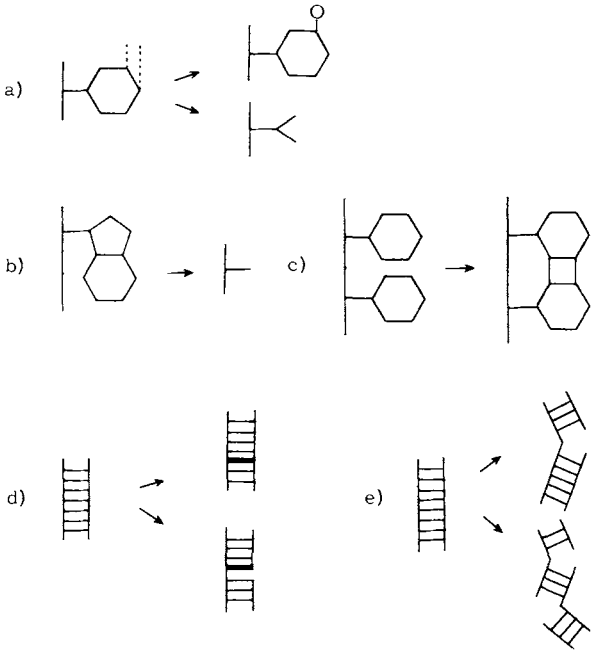

Fig. 1. Modifications which inactivate DNA (according to ref. [26]). (a) Modification of base, caused by hydroxylamine, hydrazine, methylene blue, acridine orange. (b) Removal of base, caused by hydroxylamine, hydrazine, high temperature, alkylation, alkali. (c) Dimer formation, caused by UV light. (d) Crosslinks, caused by nitrous acid, UV light, mitomycin, Nitrogen Lost, low pH. (e) Single-chain breaks, caused by ^{32}P, X-rays, methyl methanesulfonate, radicals in general.

Figure 1 shows modifications in DNA leading to an inactivation, *i.e.* inability to reduplicate. Unlike the effects of mutagenic substances, the modifications inactivating the DNA can be lethal unless repaired or compensated. In this respect it should be mentioned that many of the substances causing modifications inactivating the DNA are known to be carcinogenic.

[*] $\widehat{TT}$, $\widehat{CT}$, and $\widehat{CC}$ are referred to collectively as "dimers" in the present article.

In 1958, *Hill*[27] isolated a mutant B_{s-1} from the radiation-resistant *E. coli* B/r that is 50 to 100 times more sensitive to UV light (see Fig. 2) than the parent strain. Another UV-sensitive strain was isolated by *Howard-Flanders et al.*[29] from *E. coli* K 12. These strains are unable to eliminate damage (dimers) caused by the action of UV light on the DNA. The nature of the biochemical defects in these UV-sensitive mutants was established independently by *Setlow* and *Carrier*[30] and by *Boyce* and *Howard-Flanders*[31] in their classical experiments. The bacteria were grown on a culture medium containing ^{3}H-thymine, and this was incorporated into the DNA. The cells were then irradiated with UV light, whereupon equal quantities of thymine dimers were formed in the wild type and in the mutant. On further growth of the bacteria (now on a medium containing no ^{3}H-thymine) it was found that the radioactivity decreased in the DNA of the wild type and appeared in low molecular weight fractions. Hydrolysis and chromatographic separation of these low molecular weight fractions yielded thymine dimers. These dimers were undetectable in the case of the UV-sensitive mutants, *i.e.* the mutants lacked the enzyme for the elimination of the thymine dimers from the DNA.

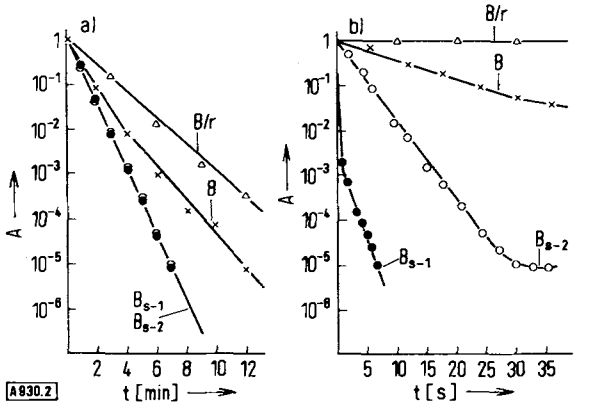

Fig. 2. Fraction A of survival rates of several *E. coli* strains (a) after exposure to X-rays and (b) after UV irradiation (according to ref. [28]).

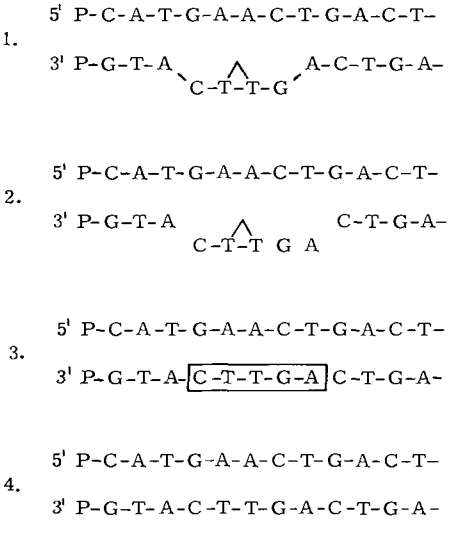

Fig. 3. Scheme of the dark repair of DNA (cut and patch mechanism); for explanations see text.

In the dark repair process the damaged part is completely removed from the DNA, whereas in the photoreactivation process the dimers are split within the DNA molecule into the monomers. Dark repair therefore involves the following steps:

1. Incision of the DNA strand at the damaged position (endonuclease reaction);

2. Excision of the damaged part (exonuclease reaction);

3. Insertion of nucleotides into the resulting gap, with the complementary undamaged DNA strand as a template (polymerase reaction, repair replication);

4. Joining of the phosphodiester bonds in the repaired DNA strand (ligase reaction).

2.2.1. Endonuclease Reaction (Incision)

Extracts from *Micrococcus lysodeikticus* and *Neurospora crassa*[32] cause the formation of single-stranded breaks in DNA containing dimeric pyrimidine derivatives; the number of chain breaks formed roughly corresponding to the number of dimers[33]. The number of endonucleases isolated from *E. coli* alone has now increased to about 4 or 5[34-40,40a,69]; however, not all of them are absolutely specific for a DNA containing dimeric pyrimidine derivatives.

An endonuclease which in fact appears to play a role in repair processes on DNA was isolated by *Kaplan et al.* from *Micrococcus luteus (M. luteus)*[41], and its properties were investigated[41]. The enzyme seems to be specific for UV-irradiated double-stranded DNA in *in vitro* experiments, and has a Michaelis-Menten constant (K_m) of 1.25×10^{-5} mol/l for this substrate. Native DNA, irradiated denatured DNA, and unirradiated denatured DNA are not attacked by this enzyme. On the other hand, native DNA irradiated with γ-rays (^{60}Co) is an appropriate substrate[41a]. With this DNA it was demonstrated for the first time that the enzyme is not absolutely specific for UV-damage only. The molecular weight of the enzyme is 15000. In the UV dose range of 10^4 to 10^5 erg/mm^2, a linear relation exists between the number of dimers formed and the number of single-chain breaks, *i.e.* one chain break is formed per dimer. The curve is very similar for DNA from *E. coli* and from *M. luteus*; the only difference seen is in the reaction rate (Fig. 4), possibly as a result of a lower dimer content in the *M. luteus* DNA.

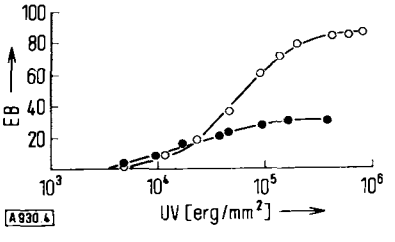

Fig. 4. Formation of single-chain breaks (EB) by the endonuclease from *M. luteus*, expressed as pmoles of phosphodiester bonds cleaved. The substrate was ^{32}P-labeled, UV-irradiated *E. coli* (o — o) and *M. luteus* DNA (• — •) (according to ref. [42]).

This UV endonuclease hydrolyzes a single phosphodiester bond in the 5′ position to form the photoproduct. This gives a free 3′-phosphate group on the DNA and a 5′-OH group either on the photoproduct itself or one nucleotide away from the photoproduct. However, hydrolytic cleavage does not split off any nucleotides from the DNA chain; for this a UV exonuclease is required (see Section 2.2.2). The purification of the UV-specific *M. luteus* endonuclease was recently also described by *Nakayama et al.*[43]. These findings provide substantial support for the required ability of the enzyme to "recognize" modifications in the DNA.

Very similar properties are shown by an endonuclease from T4-infected *E. coli*[39]. This enzyme is also specific for UV-irradiated DNA; native or denatured DNA are not attacked. The enzymes from *E. coli* and from *M. luteus* are activated by Mg^{2+}, but are not strictly dependent on these ions[39,42].

The UV-specific endonuclease is necessary for the *in vivo* repair processes on the DNA, as was recently shown with *M. luteus* mutants[44]. Whereas the wild type exhibited a 100% survival rate after UV irradiation, the survival rate for the mutant $Uvr_7^-end^-$ was about 0.01%; no endonuclease activity was detectable in this mutant (Fig. 5). However, there are also mutants that exhibit 100% survival rates despite low endonuclease activities or (for other *M. luteus* mutants[45]) low UV sensitivity despite a total absence of endonuclease activity.

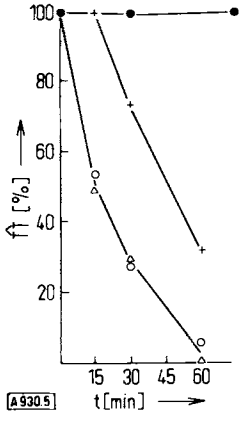

Fig. 5. Removal of thymine dimers from the DNA of the *M. luteus* mutants $Uvr_7^-end^-$ (●···●), $Uvr_{170}^-end^-$ (+—+), $Uvr_{200}^-end^+$ (△—△) and of the wild type (○···○). The strain $Uvr_7^-end^-$ has no endonuclease and does not remove dimers; the wild type and $Uvr_{200}^-end^+$ removed practically all dimers within 60 min (according to ref. [44]). *t* is the time after UV irradiation.

Though the UV endonuclease is specific for UV-irradiated native DNA, it is not known what special region on the irradiated DNA is recognized by the enzyme. If dimers are absolutely necessary for the activity of the enzyme, it is difficult to understand the repair processes observed after the action of *e.g.* methyl methanesulfonate, mitomycin, and HNO_2, unless there are other endonucleases for this purpose. An endonuclease II from *E. coli* that attacks only alkylated DNA, but not irradiated DNA, has in fact been detected[46]. It is more probable, however, that the endonucleases recognize the steric deformations caused by the agents mentioned in the DNA. They would thus have a more general function in the dark repair.

2.2.2. Exonuclease and Polymerase Reaction (Excision Repair)

After the single-chain break has been inserted (incision), the thymine dimer or the modified base is split off by an exonucleolytic reaction. An exonuclease isolated from *M. luteus*[41,42] particularly degrades those DNA sections in which single-chain breaks have been formed by endonucleases. The enzyme hydrolyzes unirradiated and irradiated, heat-denatured DNA from *E. coli in vitro*; native DNA, irradiated native DNA, and RNA are not attacked. K_m for irradiated denatured DNA is 4.5×10^{-6} mol/l[42]. Unlike the UV endonuclease, the activity of the UV exonuclease depends on the presence of Mg^{2+} ions. For each single-chain break, about seven nucleotides are split off by hydrolysis in *E. coli* DNA, and about ten in a DNA from *M. luteus*. Oligonucleotides are liberated first, and these are then degraded by the same enzyme to 5′-mononucleotides (see Fig. 6). Such oligonucleotides (containing the thymine dimers) were also detected by *Setlow* and *Carrier*[30] for the first time in their fundamental experiments.

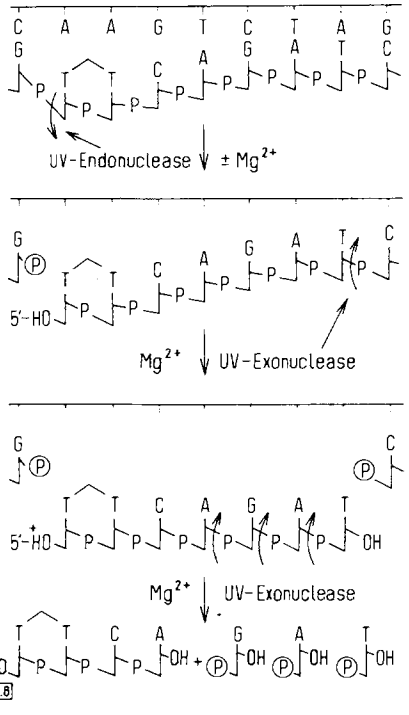

Fig. 6. Mode of action of the UV-specific endonuclease and exonuclease from *M. luteus* (according to ref. [42]).

In the gap left in the DNA by the exonuclease reaction, a free 3′-phosphate group is formed on one side (by the endonuclease reaction), and a 5′-phosphate group on the other side. The degree of degradation of the DNA differs widely among various bacteria and their mutants. In the extremely radiation-resistant *Micrococcus radiodurans* (100% survival rate even after 500 krad of X-rays), up to 20% of the DNA may be degraded (cf.[28]). Despite this considerable degradation, single-stranded DNA has not been detected in any strain of bacteria. The gap formed in the DNA by the combined action of endonuclease and exonuclease is obviously repaired immediately *in vivo* by a *de novo* DNA synthesis.

There are several known exonucleases[47,69] which degrade DNA from various sources, but according to recent investigations of the DNA polymerase, it is doubtful whether the exonuclease reveals its action in the repair process separate from the polymerase.

Thus *Kelly et al.*[48] have shown that the DNA polymerase from *E. coli* contains an exonuclease activity, which is an integral component of the polymerase and not that of an accompanying exonuclease. This DNA polymerase, which was used in the Kornberg laboratory, exhibited a 5′→3′ exonuclease activity on irradiated polydeoxythymidylic acid as a model substrate, the thymine dimers being removed in the form of oligonucleotides.

Oligonucleotides were also found after treatment of an irradiated *E. coli* DNA with DNA polymerase. After formation of a "nick" by a pancreatic DNase[48] the action of DNA polymerase liberated oligonucleotides with a chain length of 3—8 which contained the thymine dimers. An exonucleolytic activity has also been detected in the *M. luteus* DNA polymerase[49]; the exonuclease also attacks the DNA from the 5′ end, and in this case dinucleotides are formed.

In the Kornberg laboratory it was possible to separate the exonucleolytic activity from the *E. coli* DNA polymerase by partial proteolysis of the highly purified polymerase[50,51,51a,51b]. The complete enzyme has a molecular weight of 109000. Two fragments are formed after proteolysis: a large fragment (mol.wt. 76000) which retains the polymerase activity and a 3′→5′ exonucleolytic activity, and a small fragment (mol.wt. 36000) which retains only the 5′→3′ exonuclease activity[51a,51b].

The large fragment carries out DNA synthesis on nicked double-stranded DNA without degradation of the strand ahead of the growing point. It further catalyzes a 3′→5′ exonuclease action on both single- and double-stranded DNA with production of mononucleotides. Hence, this large fragment has the polymerase activity to fill the gap.

The small fragment has the 5′→3′-exonuclease activity to produce the gap in the nicked DNA. The enzyme excises mismatched DNA regions such as thymine dimers, and it can degrade DNA to mono- and oligonucleotides. Nucleoside triphosphates, which support polymerization, fail to stimulate the exonuclease. At a locus of the nick in DNA, the two fragments bind adjacent to one another to perform the coordinated exonuclease-polymerase function that characterizes the intact enzyme.

It is suggested[51c] that the 3′→5′ exonucleolytic activity of the large fragment is to remove mispaired nucleotides which have been incorrectly incorporated into the repaired DNA. Therefore, the 3′→5′ exonuclease may serve a proofreading or error correcting function; this would promote the polymerase to a wonder enzyme.

After excision of the damaged part of the DNA by the exonuclease, the appropriate nucleoside triphosphates are inserted in the resulting gap in the DNA in the 5′→3′ direction by the DNA polymerase in an almost simultaneous reaction[52]. The complementary strand acts as a template. This replication process has been described in detail by *Kornberg*[52], and will not be discussed again here.

The above-mentioned process of almost simultaneous excision and repair (excision repair, cut and patch[53,54] (Fig. 7)) seems to correspond well to the repair processes *in vivo*, and would explain the non-occurrence of single-stranded DNA in this process. The polymerase-free UV exonuclease isolated by *Kaplan et al.*[41,42] also appears to be part of an exonuclease-polymerase enzyme complex *in vivo*. *Harwood et al.*[49] detected dinucleotides as products of an exonucleolytic activity of the *M. luteus* DNA polymerase, and *Miller* and *Wells*[49a] could demonstrate and characterize an exonucleolytic activity in the *M. luteus* polymerase. It is possible that during the earlier[41,42] isolation and purification procedures this complex had dissociated into its components.

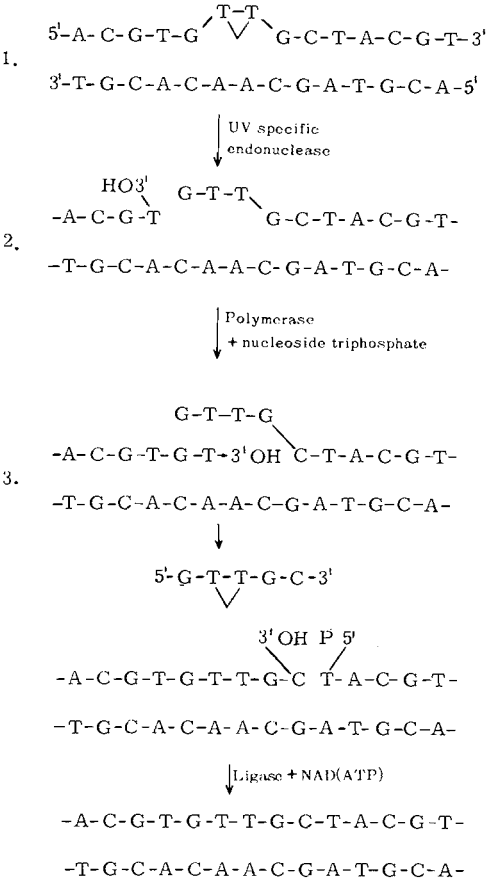

Fig. 7. Scheme of the cut and patch mechanism (cf. also Fig. 3). The gap formed in the DNA is immediately refilled.

A discovery by *DeLucia* and *Cairns*[55] first raised doubts as to whether the Kornberg polymerase is actually necessary for genetic replication and whether this enzyme might have the function of a repair enzyme *in vivo*. *DeLucia* and *Cairns*[55], and somewhat later other groups[56-61], were able to isolate mutants of *E. coli* that contained no DNA polymerase activity (measured by the incorporation of nucleoside triphosphate into DNA). These mutants (pol A1) grow quite well without DNA polymerase and reproduce their DNA in the normal way. They do this with DNA polymerase II[62-64] or DNA polymerase III[62,65] but without polymerase I (Kornberg enzyme). These mutants exhibit a strikingly greater sensitivity to UV light than the parent strains[55,58-60] (see Fig. 8).

This higher UV sensitivity is therefore due, at least in some cases[58-60], to the fact that these mutants lack parts of the enzyme system (particularly polymerase I) by which dimers are eliminated from the DNA. It seems that the DNA polymerase I is not essential for the normal replication of DNA, and actually plays the role of the repair enzyme.

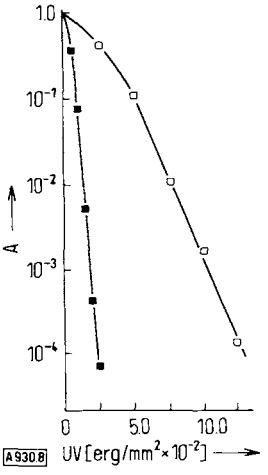

Fig. 8. Fraction A of surviving rates of *E. coli* wild type W 3110 (□—□) and mutant P 3478 (■—■), which has no polymerase I (=Kornberg enzyme) (according to ref. [59]).

2.2.3. Ligase Reaction (Joining)

The final step of the repair process is a formation of the phosphodiester bond between the newly inserted DNA segment and the old DNA strand (see Fig. 7). An enzyme which links preformed polynucleotides to one another by phosphodiester linkages was discovered in bacteria in 1967 almost simultaneously by several groups: linkage of a covalent bond and hence formation of circular DNA in *E. coli* infected with λ phages[66], healing of single-chain breaks in T4-infected *E. coli*[67], and finally enrichment of a "polynucleotide-joining enzyme" from *E. coli*[68]. This enzyme, which is usually referred to as DNA ligase, has now been detected in several organisms and purified[69], and its mode of action has been elucidated. Whereas all the ligases investigated so far are specific for the same DNA substrates and form the same DNA end products, there is an interesting difference between the enzyme from *E. coli* and the other ligases in their cofactor requirement. While the *E. coli* enzyme requires nicotinamide adenine dinucleotide (NAD)[70,71], the phage-induced ligases and the mammalian ligases require adenosine triphosphate (ATP) as a cofactor[72-74].

The mode of action of the DNA ligase is shown in Figure 9. In the first step of the reaction, the enzyme reacts with ATP or NAD, with formation of the enzyme-adenosine monophosphate complex (E-AMP) and inorganic pyrophosphate (PP_i) or nicotinamide mononucleotide (NMN). In the second step, E-AMP reacts with a DNA chain to form a pyrophosphate linkage, the 5'-phosphate group of the DNA reacting with the phosphate group of the AMP. In the final step, the bond is formed by the enzyme, and AMP is liberated.

The ligase-AMP complex (E-AMP in Fig. 9) has been identified by normal separation methods in *E. coli* and in T4-infected *E. coli*[73,75-77]. The bond between the enzyme and the AMP is covalent; *Gumport* and *Lehman*[78]

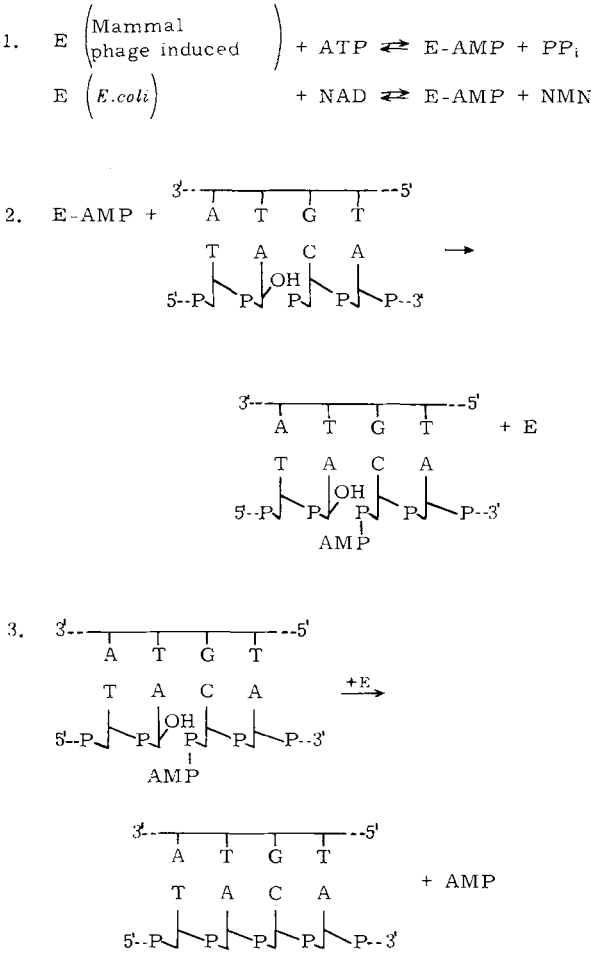

Fig. 9. Mode of action of DNA ligase (according to ref. [69]).

were recently able to show that the AMP is linked *via* its phosphate group to an ε-amino group of lysine on the ligase molecule *(E. coli)*.

In a strain of *E. coli* that requires NAD for its growth, but was grown for 2.5 h without NAD, the ligase activity is normal[78a], but the DNA synthesis is disturbed. Addition of NAD to the culture medium immediately normalizes the DNA synthesis.

The DNA-AMP intermediate has also been detected, though with some difficulty[79].

A double-helix structure of the DNA with a single-chain break is necessary for the ligase to reveal its enzymatic activity, and a 3'-OH and a 5'-phosphate group must be in adjacent positions[68,71,73]. There is apparently no specificity for a particular nucleotide[80]. The enzyme can repair all kinds of single-chain breaks, independently of how they were formed[69], provided that the above conditions are satisfied. These conditions are apparently also satisfied if two complementary DNA strands are linked to form a circular DNA[66,81,81a], as shown in Figure 10. Finally it should be mentioned that the ligase played

an outstanding role in the excellent syntheses of the alanine transfer RNA (t-RNA^{ala}) in *Khorana*'s laboratory (cf.[82]).

A series of mutants with more or less highly modified ligase activity have recently been isolated. *Pauling* and *Hamm*[83,84] isolated a heat-sensitive and radiation-sensitive *E. coli* mutant that can remove dimers from its DNA

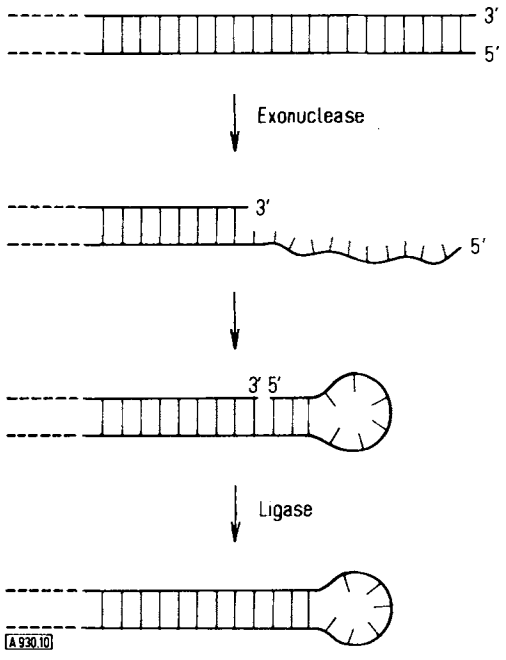

Fig. 10. Formation of circular DNA by exonuclease and ligase in *E. coli* infected with T4 phages.

and refill the gap; however, this does not give normal DNA, but relatively small DNA fragments[84]. This mutant lacks the DNA ligase. Three other *E. coli* mutants[85] contain ligase activities of 40—150% at 30 °C, but only 4—14% at 42 °C. In two of these mutants, the quantity of the enzyme-AMP complex (see Fig. 9) was decreased, and the third mutant (150% activity at 30 °C, 4% at 42 °C) was UV-sensitive at 42 °C. As was found by *Modrich* and *Lehmann*[86], a thermolabile ligase is formed in heat-sensitive mutants. Thus, not only the quantity, but also the quality of the enzyme can vary.

2.2.4. *In Vitro* Repair of a DNA

One of the (rare) prized moments in the life of a biochemist is the complete *in vitro* simulation of an *in vivo* process. A group of Dutch workers[87] recently succeeded in carrying out the entire repair process *in vitro* with the aid of the purified enzymes: ^{3}H-labeled DNA from *Bacillus subtilis* was exposed to UV radiation *in vitro*, with the result that dimers were formed in the DNA. This damaged DNA was incubated with UV-specific endonuclease from *M. luteus* (see Section 2.2.1), whereupon the DNA was incised on the 5' side of the dimers. The DNA was then incubated with DNA polymerase from *E. coli*, the triphosphates of the four DNA bases, and DNA ligase from *E. coli*. The DNA was subsequently either assayed for biological activity (transforming ability), or it was hydrolyzed and the quantity of dimers removed in the repair process was determined by chromatography.

With this *in vitro* repair, it was possible to restore 50% of the biological activity of the irradiated DNA; about 25% of the dimers were removed from the DNA under these conditions. The entire process could be performed despite the fact that the components of the *in vitro* repair system originated from different sources (*B. subtilis*, *M. luteus*, *E. coli*). When pancreatic DNase was used instead of the UV-specific endonuclease for the endonuclease reaction, no biological reactivation of the DNA occurred, *i.e.* no dimers were removed from the DNA; this is an indication of the specificity of the endonuclease.

2.3. DNA Repair in Mammalian Cells

Mammalian cells were also investigated for their DNA repair capacity. Though only few investigations have been published, the observations so far leave no doubt that this process also occurs in cells of higher organisms.

DNA breaks induced by X-rays in leukemia cells[88,88a], UV-induced DNA changes in "Chinese hamster cells"[89,90,92], and DNA damage induced by UV and X-rays in HeLa cell cultures[93], mouse fibroblasts[94], lymphoma cells[95], and human cell cultures[96,97,97a,97b] are repaired. Alkylated DNA from HeLa cells can also be repaired[91]. The processes involved in these repairs in mammalian cells appear to be fundamentally the same as in microorganisms. Dimers were removed from UV-irradiated DNA with the aid of DNA exonuclease III and IV from rabbit cell nuclei[98]. ATP-dependent ligase from lymphoma cells[74] repairs the DNA in the same manner as does the *E. coli* enzyme.

2.4. DNA Repair in Man (Xeroderma Pigmentosum)

The repair of DNA in man is clearly of special interest. The fact that this process actually occurs in man was indirectly demonstrated in a rare disease, xeroderma pigmentosum. This disease is hereditary; xeroderma pigmentosum patients are extremely sensitive to sunlight or UV light. After brief exposure to sunlight they exhibit symptoms similar to those observed in normal skin after strong irradiation with X-rays, very often associated with skin tumors. The disease is not caused by the accumulation of light-sensitive products such as hematoporphyrins in the skin. It is now known to result from a genetic defect in the DNA repair apparatus.

The nature of the biochemical damage in xeroderma pigmentosum has been elucidated in particular by the investigations by *Cleaver*[99-101]. In the crucial experiment[100], the DNA repair in skin fibroblasts of xeroderma pigmentosum patients was investigated after two types of DNA damage:

1. The fibroblasts were irradiated with UV light; this leads to the formation of dimers, especially thymine dimers, but no chain breaks.

2. The fibroblasts were first irradiated with X-rays, which cause chain breaks but no dimers, and then with UV light, which in addition gives dimers.

In the first case all three repair steps, *i.e.* incision of the DNA (Section 2.2.1), exonuclease and polymerase reaction (Section 2.2.2), and ligase reaction (Section 2.2.3), are necessary for the repair of the resulting damage. The first step is unnecessary in the second case, since the incision (= chain breakage) has already been effected by the X-rays.

It was found that the only fibroblasts that can perform a DNA repair are those in which chain breaks have been produced as well as thymine dimers (case 2). Fibroblasts in which only dimers have been produced (case 1) cannot repair their DNA.

It was thus shown (a) indirectly that DNA repair occurs in man and (b) directly that xeroderma pigmentosum patients lack the UV-specific endonuclease.

The same results were obtained somewhat later by *Setlow et al.*[102]. These authors were able to show that normal fibroblasts remove 70% of the dimers from the DNA in 24 hours, with simultaneous appearance of single-chain breaks, which then disappear again. In fibroblasts from xeroderma pigmentosum patients, less than 10% of the dimers are removed from the DNA; the appearance and disappearance of single-chain breaks was not observed in this case. Meanwhile, the technique for the measurement of DNA repair in human cells has been developed to a considerable degree of perfection[103].

It has been mentioned that skin cancer occurs very readily in xeroderma pigmentosum patients. It is possible that the accumulation of dimers and other products in the DNA of the skin cells leads directly or indirectly to the transformation of these cells into cancer cells or predisposes them for this transformation[102]. In any case, it was possible to show here for the first time that dimers *per se* have something to do with carcinogenesis.

3. Genetic Recombination

The investigation of repair processes on DNA is not merely a hobby for radiologists; they also appear to make possible another process that occurs widely in nature, *i.e.* genetic recombination. In this process, two chromosomes break and rejoin crosswise (see Fig. 11). For this process to occur, chain breaks must be produced, parts of the DNA must be removed and new parts synthesized, and phosphodiester linkages must be formed. The processes involved are thus fundamentally the same as in the repair process, of course without the removal of dimers.

It is uncertain how the breaks occur in the DNA (chromosome) during the recombination. Breaks of this type evidently cannot be repaired immediately by the ligase. Endonucleases may play a role here[104]. On the other hand, it has been found that an exonuclease (phage λ) participates in the recombination process[69, 105]. Likewise, all experimental data so far[69] also suggest that the gaps that occur in the recombination process (see Fig. 11) are filled by a synthesis of new DNA (on the complementary strand). The phosphodiester bond is evidently formed, as the final step of the recombination process, by the same DNA ligase as in the repair of UV-damaged DNA[69]. Though there are only a few experimental results supporting the idea that DNA repair and genetic recombination are catalyzed by the same enzyme system, no data have

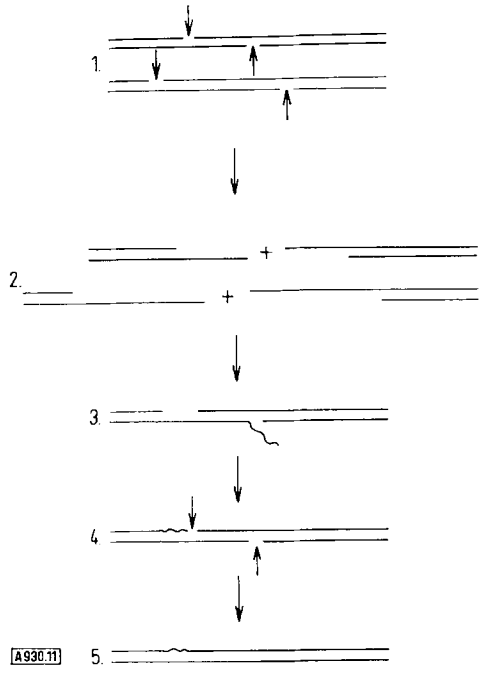

Fig. 11. Scheme of genetic recombination. A chain break is formed in the first step (cause unknown). In the second step, the double helix unwinds, and complementary nucleotide sequences are exposed. In the third step, homologous regions of the two DNAs join to form recombined double strands, which still have gaps and overlapping segments. The gaps are refilled (repair replication) and the overlapping segments are split off by hydrolysis (exonuclease) in the fourth step. The remaining single-chain breaks are repaired in step 5 by formation of a phosphodiester linkage (ligase). The recombined molecule is a DNA double helix consisting of parts of the two parent DNAs.

so far accrued which principally contradict this concept. This view is further supported by the fact that recombination-negative mutants (rec$^-$) are much more sensitive to UV light[7] than the parent strains.

4. Closing Remarks

Though most of the observations described here came from *in vitro* experiments, there is no doubt that the *in vivo* DNA repair is performed by the same mechanism. It appears however—at least in *E. coli*—that there are two DNA repair systems, only one of which requires the polymerase I (Kornberg enzyme)[106]. The *E. coli* mutants (pol A1) isolated by *DeLucia* and *Cairns*, which have no polymerase I, are more sensitive to UV light than the parent strain, but still show considerable survival rates after the irradiation process. These mutants have a second repair system, which is genetically defined as the "recA pathway" and is also necessary for genetic recombination[7]. With this system, pol A1 mutants can eliminate UV-induced dimers from their DNA. The nature of this gene product is unknown; it must be an enzyme that differs from polymerase I. The investigations by *Cooper*

and *Hanawalt*[107] support the concept that polymerase I (Kornberg enzyme) is involved in the short patch repair process of damaged DNA, while the rec-system produces predominantly large patches. Either of these systems is capable of completing the excision-repair process in the absence of the other. This could explain the survival rates of some pol Al strains on UV irradiation.

Of course, geneticists tried to produce a double mutant, pol Al rec A^{-}[108], but without success; such a mutant is apparently not viable. Thus either polymerase I or the rec A gene product is absolutely essential to growth. This means[108] that gaps occur in DNA strands during normal growth and normal division of *E. coli*, and are immediately filled.

Besides the numerous problems concerning genetic regulation of the repair process, it is not clear how the DNA-repairing system "recognizes" that there is damage to be repaired on the large DNA molecule. Probably the enzyme recognizes a structural deformation on the DNA molecule. Does a mechanism exist which transports the repair enzyme back and forth on the DNA molecule? Considering the high degree of coiling of the DNA within the cell, however, this idea would overtax the imagination even of molecular biologists.

The repair system operates with an extremely high degree of fidelity but there is evidently some tolerance for errors as no mutations would otherwise occur and this would lead to an evolutionary dead end. The repair process on the DNA is apparently also subject to selection during evolution.

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Toxicological Problems Relating to Changes in the Environment[**]

By D. Henschler[*]

Assessment of the toxicological risk from foreign substances in the environment is based on the determination of action thresholds below which effects injurious to health no longer occur, even with life-long intake. According to the latest theories it is likely that such thresholds exist even for "irreversible" (carcinogenic, mutagenic) effects. However, the difficulties besetting the determination of threshold values by experimental or epidemiological methods still appear to be virtually insuperable. The problems are both quantitative (excessive numbers of animals and observations required) and qualitative (poor predictability of effects owing to substantial differences in biological reactivity between species). Neither animal experiments nor experience with human subjects can guarantee total security from toxic effects. Legislative measures designed to restrict the introduction of chemical substances into the environment must therefore be based on compromise. Scientists must be consulted, but ultimately the decisions must be political, and politicians have to assume the responsibility for them.

1. Introduction

Civilization and progress unavoidably interact with the turnover of substances in nature. According to recent estimates[1], chemical synthesis adds some 250000 new chemical compounds each year to the two million already in existence. Roughly 300 of these new compounds are released every year into the environment, some controlled, some not. Many of them are biologically active, sometimes not intentionally, but often as the deliberate and desired result of the chemical synthesis, *e. g.* in the case of pesticides, disinfectants, food additives, cosmetics, and, by no means least, drugs.

In addition to these planned, or at any rate conscious, chemical changes in the environment, there are many unwanted ones: waste products from power stations and domestic fuel, from traffic and chemical plants are discharged primarily into the atmosphere, water, and soil. Many of these waste products have characteristics that are potentially harmful to man. Contamination is widespread in some cases, even global in others, and control measures are either ineffective or only partially successful.

However, in the course of its development mankind has always been exposed to toxic substances in the environment, and in many instances the progress of civilization has in fact led to a reduced uptake of such ancient poisons. Consider, for example, the amounts of carbon monoxide inhaled by cavemen in prehistoric times—considerably greater than those to which today's traffic policeman is exposed in the city center; think back to those clouds of street dust, the smoke from badly drawing stoves, the putrefaction products invariably present in foodstuffs, or the uncontrollable contamination of drinking water in even small settlements by organic and mineral pollutants.

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In other words, progress has not brought about any fundamentally new situation as regards the effect of environmental poisons on man. If one recalls that the most powerful toxic substances are of natural rather than synthetic origin, then one finds that from the toxicological standpoint the present environmental situation is characterized essentially by a shift in the circumstances. Any toxicological assessment of environmental changes must proceed from the starting point. Moreover, a substantial proportion of precisely the most widespread, supposedly purely man-made, environmental poisons have recently been shown to be natural constituents of the environment, in particular of the atmosphere: for example, nitrogen oxides (NO and NO_2), ozone, sulfur dioxide, carbon monoxide; indeed, traces of the latter are produced in the course of human metabolism. As regards carcinogenic substances, the most active are produced in nature and not in the laboratory. It is still difficult to say whether the march of civilization has on balance increased or decreased the hazards to human life and health from the environmental poisons.

What is certain is that the continuing large-scale introduction of new synthetic materials has multiplied the *number* of potential dangers, and is still doing so all the time. Therefore, in attempting to redress the balance and control the adverse effects of progress, we must begin by analyzing the nature and the extent of the risks to health from individual substances as well as their combined effect.

It is the function of toxicology to detect and quantify damage to health produced by chemical substances, thus paving the way for systematic preventive measures. This branch of science therefore assumes a key position in the study and protection of the environment. Animal experiments constitute its most important tool. The detection and quantitative determination of poisons are also pursued by the techniques of analytical chemistry. Experience with patients and with healthy human subjects is indispensable to confirm, or indeed cast doubt on, the results of animal experiments. Some time ago toxicology was concerned almost exclusively with the investigation of acute poisoning and the development of effective methods of treatment.

In purely quantitative terms this type of work is today outweighed by analyses of chronic poisoning effects, although its practical importance is now if anything greater than ever before.

2. Improvements in the Detection and Treatment of Acute Poisoning

A rise in the incidence of accidental intoxication has been observed for some decades as a result of the industrial and domestic use of countless cleaning and maintenance agents and adhesives, the large-scale application of pesticides, and—by no means least—the liberal recourse to therapeutic drugs. Spurred on by the good examples set abroad, the Federal German authorities have also come to recognize that a determined effort to improve diagnosis and therapy can bring about a decisive fall in the number of fatalities. Since 1965 the Federal Health Bureau's commission on the "Detection, treatment, and prevention of poisoning" has been systematically seeking out potentially toxic household products and classifying them according to the active principles. At the same time intensive-care units have been established, which can provide immediate advice to physicians handling emergencies, and if necessary take over the treatment. A confidential file compiled by the above-mentioned commission contains a list of household products and active substances, together with information on symptoms, toxic doses, recommended treatment, and chemical detection methods[2].

In the modern approach to the treatment of poisoning, *nonspecific measures* such as anti-shock therapy, oxygen, hemodialysis, and forced diuresis are more important than the administration of specific antidotes. Nevertheless, the latter are still essential in some types of poisoning that take a particularly rapid and serious course, where they

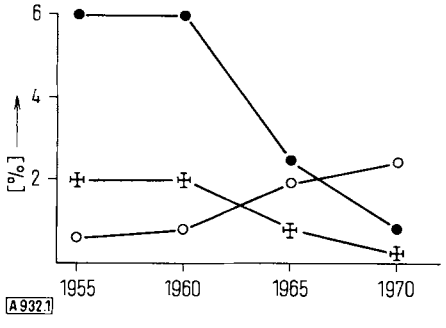

Fig. 1. Frequency of poisoning in children and the results of treatment (○—○): percentage of approx. 4000 hospitalizations per annum; (●—●): permanent injury; (✠—✠): fatal outcome (Universitäts-Kinderklinik Freiburg/Br., 1955—1970). After [3].

represent the sole life-saving remedy, for instance in poisoning due to cyanide, alkyl phosphates, or many heavy metals. Intensive care is costly in terms of both staff and equipment, and it is no doubt for this reason that many treatment centers in the German Federal Republic have not yet attained the desirable and internationally accepted standard of equipment. This situation is due to a failure on the part of authorities responsible for health policy, and must be quickly put right. Nevertheless, the decision to steer a course including both counsel and action has proved right. The fatalities due to acute poisoning (Fig. 1) have fallen to a low level, a gratifying reduction being noted particularly in delayed complications and permanent damage. It is thus possible to make satisfactory headway in this area, provided that adequate funds can be made available.

3. Long-Term Effects of Small Amounts of Environmental Poisons

It is much more important, and at the same time also far more difficult, to evaluate the long-term effects of very small doses or concentrations of potentially toxic environmental substances on large populated areas. This has in fact become the principal task of modern toxicology. A selected listing from among the large number of man-made environmental pollutants with largely known toxic action potential is presented in Tables 1 and 2. The latter give substances which are distributed widely or even globally, and which are or may be responsible for particular forms of injury to health.

It would be outside the scope of the present paper to attempt an exhaustive survey of the current status of toxicological knowledge concerning each substance, and the reader is referred to the literature for such details[4]. Mention must, however, be made of the distinction between the suspected and certain toxic effects of the individual substances under the currently prevailing environmental conditions, a distinction that emerges from a critical analysis of the present state of knowledge. Only in the case of a few of the substances listed can injury to the health of at least some of those exposed be regarded as certain. In this context no account is taken of isolated and limited cases of poisoning due to accidental contamination of the environment. Even where the effects are certain, they may show extreme variations in magnitude, not only as regards the frequency of occurrence, but also their nature: For example, a measurable, but quantitatively insignificant formation of methemoglobin due to nitric oxides, or of carbon monoxide hemoglobin due to carbon monoxide, represent no real pathological threat under normal environmental conditions, whereas the slightest rise in the incidence of cancer is of the gravest importance. However, it will be seen from the tables that, with the one exception of asbestos, suspected carcinogenic effects have not been confirmed (occupational cancer due to chemicals is not taken into account here).

There is no sound scientific basis for the statement recently made by a cancer researcher[5]—and incidentally widely misquoted and misinterpreted in the lay press—to the effect that 90% of all cancers in man are attributable to chemical carcinogens and 50% to environmental factors. It is also worth pointing out that closer scrutiny of findings relating to the effects of pollution on man frequently produces surprising results: For instance, the concentration of mercury in the Atlantic off the coast of North America has not changed for centuries[6]; a survey carried

Table 1. Effects of man-made inorganic environmental poisons.

Substance	Occurrence [c]	Toxic effects suspected	Toxic effects confirmed	Trend in environmental loading
Arsenic [a]	F, D, O	carcinogenic		↓
Asbestos	A, F, D, O		carcinogenic	↑
Lead [a]	A, F, O	blood damage, neurotoxic, mutagenic		↑
Cadmium [b]	F, O	nephrotoxic, hypertensive, carcinogenic		↑
Fluoride [b]	A, D, O	bone hardening	dental damage	→
Carbon monoxide [a]	A, O	neurotoxic	blocking of blood pigment	↑
Nitrate/nitrite [a]	F, D	formation of carcinogenic *N*-nitroso compounds		↑
Nitrous fumes (NO,NO_2)	A, O	lung damage, carcinogenic	formation of Met-Hb	↑
Ozone, oxidizing agents [a]	A, O	lung damage		↑
Mercury [a]	F, O	neurotoxic		→
Sulfur dioxide [a]	A, O	lung damage		↓
Vanadium [b]	A, O	carcinogenic		↑

[a] Occurring naturally.
[b] Essential.
[c] A = Air, F = Food, D = Drinking water, O = Occupational.

Table 2. Effects of man-made organic environmental poisons.

Substance	Occurrence [a]	Toxic effects suspected	Toxic effects confirmed	Trend in environmental loading
Aldehydes (automotive exhaust gases)	A	lung damage, mutagenic	eye irritation	↑
Antibiotics	F		interference with bacterial ecology	↑
Benzene	A, O	leukemogenic, mutagenic		↑
Carcinogens				
polycyclic hydrocarbons	A, F	carcinogenic, mutagenic		↑
aromatic amines	F, O			
epoxides	A, F, O			
N-nitroso compounds	F			
Hormones	F	metabolic modifications		↑
Insecticides				
chlorinated cyclic hydrocarbons (DDT)	F	carcinogenic, hepatotoxic		↓
organophosphates	F	neurotoxic		↑
Polychlorinated biphenyls	F	hepatotoxic		↑
Herbicides				
2,4,5-T (dioxine)	F	teratogenic, mutagenic		?

[a] A = Air, F = Food, O = Occupational.

out in the USA even shows that the mercury content of human organs has been falling in recent years[7].

The value of such schematic surveys may be questioned, and in some points different interpretations could be advanced. However, no attempt is being made to present a comprehensive study. They merely serve to underline the fact that at the present time suspected toxic effects vastly outnumber those confirmed. On the other hand, it is of course quite impossible to *rule out* the possibility of toxic risk in the case of the suspected effects. Moreover, even where injury to health has been demonstrated with certainty, it has been difficult to *quantify* its extent satisfactorily. Such uncertainties characterize not only environmental toxicology, but also many other areas of environmental research. It is hoped that the following attempt at an analysis of the causes will facilitate an understanding of the situation, as well as providing a basis for the development of effective measures to improve it.

4. Epidemiological Investigations

One method of establishing the risk is by epidemiological statistical analysis. This technique has brought to light a number of important, often unexpected relationships pertaining to the intensity of the exposure of man to envi-

ronmental substances, especially those which accumulate in the body, *e.g.* DDT, vanadium, mercury, lead, and so on. With one exception—namely lung cancer in smokers—these investigations have hitherto yielded little valid information concerning the nature and the extent of the actual danger to health. This has not prevented many people from making false claims as to causal relationships allegedly demonstrated in the course of epidemiological environmental research. The mistake made by authors, and even more so by those who interpret their work, resides in an assumption that their factor analysis is flawless. In reality for the investigation of large population groups factor limitations are arrived at in a more or less arbitrary manner; in fact, their admissibility can be neither demonstrated nor refuted. However, even where a relationship appears plausible, or indeed compelling, as in the case of smoker's cancer, it has still been impossible to prove causality in a scientific sense. As we know only too well, we are still far from identifying the constituent or constituents of tobacco smoke that are carcinogenic in man.

Basically, a causal relationship between the long-term action and a toxic effect can in the case of most environmental poisons be demonstrated only in model experiments under fully controlled conditions. This requirement can as a rule be satisfied only by animal experiments. The latter are in any case essential, since they provide the sole means of determining quantitative dose/effect relationships which can be used as a basis for calculating the risk. Long-term animal experiments are associated with numerous problems, particularly when it comes to toxicological investigation of the environment, and it is essential to know their possibilities and limitations if the results are to be valid. In considering them no attempt will be made at a systematic presentation of experimental details, which are fully described in the literature[8].

5. Determination of Risk by Means of Chronic Animal Experiments. The Problem of "Threshold Values"

Chronic animal experiments are organized and evaluated on the basis of two assumptions:

1) The occurrence and the magnitude of toxic effects are dose-dependent and can therefore be calculated

2) There is a threshold dose below which no toxic effect occurs. The essential aim, then, is to demonstrate the *absence* of an effect, an approach that has aptly been described as "non-toxicology". In its way, this is unique in the life sciences, for whereas researchers in other fields seek out and analyze real states and changes in these states, we are trying to determine the absence of changes, as it were the demonstration of something negative. The toxicological threshold value is used to lay down tolerance levels designed to prevent injury to human health. The determination of a threshold value for toxic effects involves problems which shake the very foundations of toxicology:

The toxic effect is dependent on the concentration (c) at the biological receptor and on the duration of exposure (t). If the product is a constant magnitude (W), we obtain a hyperbolic dependence:

$$c \times t = W$$

If the product, now taken as a variable dose, is plotted on the familiar dose/effect graph, then—because of the asymptotic approach of W to t in the above equation—the curve obtained passes through the origin. This means that neither mathematically nor fundamentally is it possible to derive a dose level at which no effect occurs. This would mean that no threshold value exists.

This concept received support through experimental investigations with ionizing radiation, which were used in the derivation of the "hit theory"[9], and through experiments with chemical carcinogenesis, in which the action product remained the same over a large concentration or dose range[10]. Further support was sought in the postulate that all that was needed was that just a single reactive molecule had to hit a "target" molecule in a biological system, as a rule in the cell, and trigger a biological effect. Hence it would be possible for no lower dose or concentration limit to exist for biological effects.

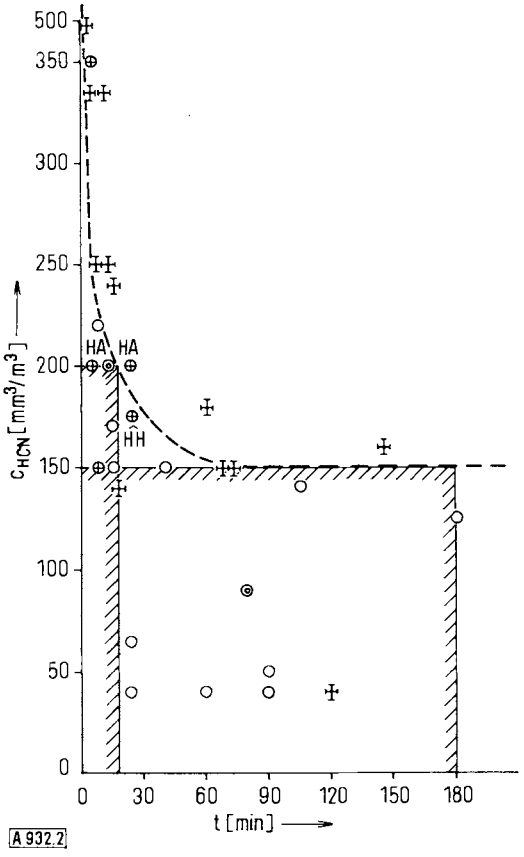

Fig. 2. Fatal effect of inhaled hydrogen cyanide as a function of the active concentration and inhalation time. Demonstration of a threshold concentration.
H = dog, A = monkey, ✣ = fatal poisoning, ○: animal survives, ◎: two animals survive, ⊕: one animal dies, one survives. After [12, 13].

On the other hand, empirical considerations and sound common sense tell us that thresholds and concentration regions with no toxic effects must exist. *Paracelsus* was

probably the first to give a clear enunciation of the action threshold in the third of his seven Carinthian defenses[11]:

"what is it that is not poison? all things are poisons/ and none that are not/ Only the dose decides that a thing is not poisonous".

The first experimental proof of the existence of a threshold of action was adduced by *Flury* and *Heubner*[12], who used hydrogen cyanide, showing that below a certain concentration the gas could be inhaled almost indefinitely without fatal results (Fig. 2). They were thus able to refute *Haber*'s rule of the constancy of the action product

$$c \times t = W = \text{const.}, \quad (1)$$

formulated on the basis of the results of experiments with phosgene. *Flury*[13] explained the later results in terms of an elimination (e) of the foreign substance or its effect, which counteracts the absorption by the body and must be subtracted from the concentration:

$$(c-e) \times t = W = \text{const.} \quad (2)$$

This elimination was later shown to be enzymatic detoxication of cyanide to thiocyanate[14].

A plausible theoretical basis for the existence of an inactive concentration, which would justify the assumption of threshold values, was recently formulated with an interesting deduction, relating also to "irreversible" (carcinogenic and mutagenic) effects[15], for which it had been emphatically rejected[16]. It is possible to estimate the proportions of

Table 3. Concentrations and estimated probability (P) of reactive atoms in liver cells. After [17].
Elements printed in bold type are essential, others are not.

Element	Atoms/cell	P
H, O	$>10^{14}$	1.0
C, N	10^{12}—10^{14}	1.0
S, P, Na, K, Mg, Cl, Ca, Fe, Si	10^{10}—10^{12}	≈0.9
Zn, Li, Rb, **Cu, Mn**, Al, Br, **F**	10^{8} —10^{10}	≈0.4
Sn, Ti, Mo, **Co, I**, Pb, Ag, B, Sr, Ni, Sc, Cd, Cr, **Se**	10^{6} —10^{8}	≈0.3
V, Hg, Be	10^{4} —10^{6}	≈0.1
40 others	10^{2} —10^{4}	≈0.1
Ra	10^{0} —10^{2}	

atoms and molecules in body cells by weight or number (Table 3)[17]. The lower limit of biological activity for trace elements is 10^4 atoms/cell. It is a dogma of biochemistry that these elements act through highly specific bonding or reaction sites. In contrast, on the basis of what we know about toxicological action mechanisms, foreign substances always have in addition nonspecific reaction sites whose number increases with the reactivity of the substance. This has been demonstrated in the case of heavy metals acting on SH enzymes[18], and for reactive carcinogens[19]. It is deduced from this that for foreign substances, as for trace elements, a certain minimum number of molecules must be present in order to give rise to a biological effect. In fact, it may be assumed that this number will be higher in the case of foreign substances than in that of trace elements. A man weighing 70 kg is made up of 6×10^{13} cells, and hence needs 8.6×10^{15} molecules/kg of cell mass as a minimum concentration of foreign substances to produce a biological effect, or, expressed in equivalents, 1×10^{-8} mol/l. Action thresholds derived on this basis for certain highly active carcinogens all range between 10^{13} and 6×10^{17} molecules/kg[20].

It must be admitted that no abstract proof can be adduced in support of a comparison of the biological effect of trace elements with the toxic effect of molecules of a foreign substance, but such comparison is acceptable on the basis of the theoretical principles of biochemistry and toxicology. This does not, of course, eliminate the fundamental difficulty of establishing action thresholds in each individual case. The deduction does, however, provide a sound basis for the acceptance of threshold values and tolerance limits in the practical assessment of risks.

The philosophy of threshold levels below which foreign substances pass through the body harmlessly, in the case also of "irreversible" effects, is further strengthened by the fact that all biochemical structures undergo permanent renewal, so that there is a possibility of changes being repaired, even when they occur in the genetic material of the cell. Moreover, all biological processes, including the restoration processes, are homeostatically controlled, so that changes can be compensated provided they do not exceed a certain magnitude. As soon as a process opposed to the biological change comes into play, the existence of an effect-free zone of concentration or dose can in fact be mathematically derived, in the sense of eq. (2).

Furthermore, there is a fundamental difference between the "value" of biological and toxic effects which is not allowed for by the "single-molecule theory": A biological process induced by foreign substances only becomes toxic when the change produced in the structure and/or function has an adverse effect on the stability and renewal of the body as a whole.

6. Predictive Value of Chronic Animal Experiments

Long-term animal experiments must satisfy three criteria: 1) the number of animals must be sufficiently large to ensure that rare effects do not escape detection; 2) toxic effects must be clearly discernible, so as to be susceptible to measurement; 3) the mode of action of the tested substance on the experimental animal and on man must be largely or completely identical if valid inferences are to be drawn from one to the other. In this connection problems arise which restrict the validity of the results of animal experiments. Although the three requirements mentioned above are satisfied in the vast majority of the substances and their effects, there are important exceptions. Difficulties arise especially where the evaluation criterion is not the strength of the effect on the individual but the incidence of an event in a group, *e.g.* the occurrence of cancer or of mutations. With an upper limit to the frequency of occurrence of only 2‰, about 1000 animals would be required for a confidence level of 90%, and about

30000 animals for 99.9%. The practical inference of this is obvious: taking the population of West Germany, two in every thousand of those aged 45 or more would mean some 40000 additional cases of cancer, or nearly 2000 per annum. The scope of the experiments, and hence the information they provide, is governed by practical limitations.

Special problems are encountered in the simulation of the manner in which the foreign substance is absorbed by man. For example, in animals it is quite impossible to reproduce the inhalation of cigarette smoke satisfactorily. Inhalation experiments with aerosols and gases are always problematic, owing to the much more effective nasal filter that animals have, the different type of breathing, and the different breathing intensity, the latter resulting from the animals' peculiar heat regulation system which is due to their fur. Hence research into the effects of atmospheric pollution suffers in many respects from the lack of suitable models.

7. Differences in the Sensitivity of Man and of Experimental Animals

The differences in the *manner* in which man and animals react to foreign substances are far more important. There are two main reasons for this: 1) the target organs vary in their susceptibility to the action of foreign substances; or 2) the foreign substance reaches the target site in a different concentration or in another form, or perhaps even not at all, because its chemical changes in the body are different. Apart from a few insignificant examples, we know practically nothing about the mechanisms of the first type. The first explanation is often advanced if the search for evidence of the alternative proves inconclusive. However, tremendous strides have been made in this area in recent times, and the study of the change of foreign substances in the metabolism and of their pharmacokinetic behavior has developed into one of the most promising fields of research in experimental toxicology. With the aid of sophisticated separation and determination techniques employing chromatography, mass spectrometry, and radiochemistry it is in some cases possible to follow the fate of foreign substances step by step as they pass through the body. Since such investigations can often be conducted even in man with safe, very low, doses or concentrations, it has been possible to establish comparability between man and experimental animals. This in turn has provided a rational basis for chronic tests and hence also substantially improved their practical usefulness. At the same time, the information acquired so far has revealed unsuspected qualitative and quantitative differences between individual species of animals, as well as between animals and man, and it is only now that the magnitude of the problem is apparent. Space does not permit a systematic discussion, and the reader is referred to the specialized literature[21]. However, the amount of work and time needed to obtain an uninterrupted pharmacokinetic profile is so huge that a systematic investigation of all environmental poisons is not likely to be completed in the foreseeable future.

The problem is further complicated by the fact that many poisons do not release toxic effects in their original form but in a chemically altered one. Although metabolic transformations often represent detoxication reactions, in many cases also inactive precursors are converted into reactive derivatives. These can be difficult to detect, especially if the proportion of the amount converted is very small in relation to that ingested; detection is frequently only possible by indirect means, owing to the instability of the chemical species concerned in the biological medium associated with their high reactivity. The limited possibility of detection restricts the predictability of the occurrence of a toxic effect, leaving an uncertainty, a question mark against the value of the toxicity test. If *pharmacogenetic* peculiarities, *i. e.* changes of the metabolic pattern in only a few genetically determined exceptions in the human group, are involved, then animal experiments must of necessity fail.

8. Carcinogenic, Teratogenic, and Mutagenic Effects

The metabolic activation mechanisms assume special importance in the case of carcinogenic, teratogenic, and mutagenic substances. The *malignant tumors* observed hitherto in man following the action of chemical substances, practically without exception occupational cancer, either form at the site of action or else, when they occur after absorption of the substance, are characterized by strict organotropism. The cancer types produced by chemical substances in the course of animal experiments are also governed by organotropism, but if we go by their localization and histological structure they are to a large extent unknown or rare in man. The organotropism can vary from one animal species to another with one and the same substance; certain compounds are carcinogenic in some species, but not in others; for example, the strongest known carcinogen, aflatoxin, has practically no effect on sheep[22]. The type of tumor frequently observed in feeding experiments involving the administration of foreign substances to mice—the officially recommended and most widely used rodent—namely a particular kind of hepatoma, is practically unknown in man. Extreme variations are observed in the frequency and indeed in the appearance of tumors at all between different series of experiments involving similar animals and substances, when the latter are administered at doses close to the threshold, since in such cases nonspecific influences of the experiment mask the effect of the foreign substance[23]. In many animal species and breeds benign and malignant tumors occur quite spontaneously, the only effect of "carcinogenic" substances being to accelerate their formation. The significance of such an acceleration with respect to the risk of cancer in man is not clear.

As long as the causes of organotropism remain unexplained, it will be impossible to *predict with certainty* that a substance shown to be carcinogenic in animal experiments can also give rise to tumors in man. Conversely, a negative finding in animal experiments *cannot rule out with certainty* the risk of cancer in man. Risk assessments relating to carcinogenic effects must therefore be reduced

to compromises not resting on a rigorous scientific basis. A committee of experts in the USA has worked out a recommendation[24] which has been adopted in many countries. According to this, every substance that has definitely given rise to tumors in animals should be regarded as carcinogenic and therefore representing a potential cancer threat to man.

Such a rule is unsatisfactory as long as the risk remains unquantified, and until its relationship with the permanent, definite carcinogens in the environment, say the 100 or more carcinogenic substances in "pure" food[25], is clarified. There is an obvious possibility, indeed a probability, of underestimating real risks and overestimating negligible ones. In tending to militate against a more accurate assessment of the situation, the recommendation also distracts our attention from the most pressing concern, namely the pinpointing of the carcinogenic substances that have no effect on rats or mice, the routinely used experimental animals.

Only exceptionally have *teratogenic* risks been associated with environmental poisons at the concentrations encountered in practice. One such instance is 2,3,7,8-tetrachlorodibenzo-*p*-dioxine, occurring as an impurity in the herbicide 2,4,5-trichlorophenoxyacetic acid[26]. The thalidomide tragedy has lent powerful impetus to the experimental investigation of teratogenesis and has led to the careful development of experimental techniques that have been subjected to scrutiny[27]. Nevertheless, the substantial biological differences between the embryonal development in man and in experimental animals means that the *predictive* value of the test methods is limited. The thalidomide case provides a good illustration of this: the malformation syndrome observed in man cannot be reliably reproduced to the same extent in animals under comparable conditions. In other words animal experiments cannot at present be used to rule out teratogenic risk with certainty.

The situation in the domain of *chemical mutagenesis* is even more problematic. Tests on primitive organisms, developed successfully for the investigation of the molecular biology principles of mutagenesis, are quite unusable for risk evaluation, since they do not take into account the pharmacokinetic behavior of the foreign substances, which can have a decisive influence on whether or not mutagenic changes occur. This applies particularly to cases in which the effect is produced not by the substances themselves but by metabolites. Lower organisms do not have the activation mechanisms found in mammals. This situation, which has long been obvious to toxicologists, was until recently totally ignored by geneticists. Indeed the general policy was to carry out routine tests on foreign substances with primitive organisms and to demand a ban on their use in the event of a positive finding[28]. With this in mind, the Deutsche Forschungsgemeinschaft established a testing laboratory. Its activities were justified among other things with the argument that the results obtained with *in vitro* methods are 99% transferable to man[29]. This claim is quite untenable, being totally bereft of all scientific basis. The fact is that on the basis of tests on lower organisms many substances are pronouncedly mutagenic which are manifestly not mutagenic in man, whereas numerous highly toxic, carcinogenic, and probably also mutagenic principles are overlooked. At this point a danger comes to light which also inhibits progress in other areas of research into toxic effects: In making things too easy for ourselves with oversimplified demands we are losing sight of the real dangers, and the analysis of the overall situation becomes distorted.

Mutagenicity tests on intact mammals have a certain value. However, they have not yet advanced to the stage where one could expect reliable data for the assessment of the risk of mutagenesis in man. In particular, further investigations are needed into the usefulness of the methods in the case of the prolonged action of low concentrations of foreign substances. Scarcely any work has been done into dose/effect relationships in this area, which is of primary importance for environmental toxicology. Systematic mutagenesis research has hitherto been carried out mainly with high, acute toxic doses of alkylating agents. The mutagenic potential of these substances is well known; after all, they have been used medically with the precise object of cell damage. The data so far available concerning the mutagenic effects of the real and important environmental poisons on man thus represent conjecture rather than scientific evidence.

9. How Safe is "Safe"?

The above discussion of the limitations of epidemiological methods and animal experiments shows plainly that it is impossible to predict with absolute certainty whether a toxic effect in man must be expected or can be ruled out with particular substances. Despite this, the authorities expect, the press demands, and many manufacturers promise "safety" from injury to health through environmental poisons. Legislators use the term "harmlessness" in laws and regulations. Both "safety" and "harmlessness" imply a guarantee, and inevitably persuade the layman that it can in fact be given. Unfortunately, biological experiments are fundamentally incapable of providing such a guarantee. In Germany, the layman's understandable desire for security is also nurtured by a linguistic misunderstanding, to which journalists are particularly prone: The English "safety" is glibly translated by "Sicherheit". In actual fact, by "safety" we mean that it is sure or likely that no harm will result[30], whereas the German "Sicherheit" denotes "an absence of danger, protection from any threat"[31].

The toxicological assessment of foreign substances must therefore always involve a greater or lesser, but never completely calculable residual risk. Toxicity tests can measure only relative safety, which must be defined according to the prevailing fund of scientific knowledge. Scientists, the press, and legislators should have the courage to acknowledge this fact and to enlighten the public as to the true state of affairs, eschewing all simplification. Laymen must learn something about biological variability and quantitative relationships, and they must realize that the use of chemicals is fundamentally inseparable from risk. Only in this way will the public be able to assume a proper share of the responsibility that the progress of civilization imposes upon us.

All the same, toxicology finds itself permanently compelled to act: Judgments have to be made under the pressure of the gravity and complexity of the problems to be solved, and frequently on the basis of inadequate data. These externally imposed shackles on the quality of judgments cast a stigma on the discipline. Compared with the clarity with which results can be obtained and interpreted in other scientific domains, the situation in toxicology gives little cause for satisfaction. Similar problems are encountered in the assessment of the environmental hazards associated with nuclear reactors. The need to compromise, to calculate the incalculable, was recently described by *Weinberg*[32] as "trans-scientific elements". Nevertheless, pessimism would be out of place. We are at the present time experiencing a period of extraordinary improvements in toxicological methods leading to better and earlier detection of toxic risks. Success in this endeavor depends, now and in the future, on a joint effort by both scientists and legislators, even though their roles are quite distinct.

10. Solutions

1. The prevention of damage to the environment and of danger to human health from pollution calls for *restrictive legislation*. The nature and scope of the latter is a purely *political* matter, but the political decisions in this area must be based on scientific advice concerning the measures that can be taken to avert a danger to health. Such advice must be confined to a statement of strictly *scientific* facts. Examination of the economic benefits and burdens associated with restrictive measures falls entirely within the province of the politician. Such considerations must not influence scientific judgment. Experience shows that if the scientist changes his mind by permitting economic factors to affect scientific decisions, legislators and press alike will be quick to discredit him. And rightly so. Yet the politician, too, should be honest enough to acknowledge the political motivation behind his decisions and not seek to cloak them in pseudoscientific arguments. Take one example: The German Federal government justifies the law banning the use of DDT by stating that whereas damage to health had not been demonstrated, it could not be excluded[33]. As already explained, however, such an exclusion cannot be demonstrated, for DDT as for any everyday food or "harmless" environmental factor. The justification is neither plausible nor practicable.

2. *Recommendations* and *decisions* on possibly toxic environmental substances should not be made by heterogeneous committees containing a small minority of members with direct practical experience of the problems of toxicity tests and their value. Majority decisions can in such circumstances be erroneous. For instance, the advisory committee which recommended the ban on DDT in the USA outvoted the argument that the animal experiments performed to test for a carcinogenic effect were grossly defective in both organization and evaluation[34]. Today everyone feels called upon to pronounce on toxic effects and the risk to health from environmental pollution; why cannot this task be left to the genuinely knowledgeable specialists working to unravel the complexities of the field, as is the case in nuclear physics or oceanology?

3. A *total prohibition* on substances whose harmful effect has not been demonstrated is not, as a rule, likely to eliminate health risks. On the contrary, it may very well increase them. For the ban leaves a gap in supply, and, in its efforts to meet the demand, industry switches to less thoroughly researched materials, concerning whose effects on man little or no experience has been gathered. These materials can therefore conceal a greater risk—or at any rate one more difficult to appraise—than the prohibited substance. Following the ban, efforts to throw light on the causal relationship are broken off, and the uncertainty in the identification of real poisons increases. Our interests are better served by effective control of the use of the incriminated substance and its restriction to the economically necessary extent, *i.e.* by *prevention of misuse* with simultaneous intensification of research into the material's ecological behavior and toxicological properties.

4. Restrictive measures should be based on a *quantitative* assessment of the risk, especially in the case of potentially carcinogenic and mutagenic substances. A substance should not be banned automatically because of evidence of a carcinogenic effect. The decision should be based on a comparative examination of the strength of this effect with due regard to the nature, intensity, duration, and frequency of action. Very weak or doubtful carcinogenic and mutagenic effects produced by man-made substances must be carefully weighed against the potential dangers of "natural" substances.

5. Discussions and judgments on questions of environmental toxicology must remain *free from emotional arguments* and global claims confined to individual disciplines. What sense can there be in, say, inflating the relative importance of mutagenetic research with statements such as: "We must not wait until the lunatic asylums are overflowing with abnormal children", or claiming, as someone did recently[35], that problems of environmental toxicology should and could be solved exclusively by mutagenicity tests?

6. Judgments in the field of environmental toxicology and the legislative measures based on them should be *re-examined at certain intervals*, and if necessary amended, to allow for progress made in the intervening period. The initial decisions should in no way inhibit subsequent correction. The soundest policy is to impose restrictions—and issue authorizations—step by step, maintaining constant surveillance to check whether the existing measures are working well.

7. Owing to the vast scope of the problems encountered in environmental toxicology, optimal use must be made of present and future *research capacity*. A comprehensive study of the toxicological action of a foreign substance can only be successfully carried out by teamwork involving not only toxicologists, but also biochemists, analytical chemists, geneticists, and if necessary also microbiologists, epidemiologists, and specialists in various aspects of general and industrial medicine, backed by all the technical resources of these domains. The interdisciplinary character

of toxicology creates a need for large and well equipped research facilities. If individual aspects of projects are assigned to laboratories with conventionally limited specialization, there is a strong risk of distorted and unqualified judgments in the interpretation of the results from the health standpoint. Whether a biological effect is a state of disease or not can in the final analysis only be evaluated by a physician. In arriving at its final verdict on a toxicological problem, a competent team would thus be led by a toxicologist combining qualifications in experimental toxicology, pharmacology, and pathophysiology with experience in clinical medicine. Regarded in this light, environmental toxicology emerges not as a conventional discipline but as a task that must be tackled jointly by the classical fields of medicine, chemistry, and biology.

8. In the interests of better comparability of the results, toxicological laboratories should be subjected to standardization and *quality control*, like in the areas of analytical and clinical chemistry. Such a policy would greatly reduce or even eliminate duplication of work.

9. The *information flow from laboratories in industry*—which is undertaking its own independent toxicological research on a growing scale, spurred on by the legislation of responsibility of the originator—represents a trickle rather than a torrent. Environmental research would benefit from an improvement in this respect. This lack of cooperation may be partially attributed to misunderstandings between representatives of the controlling authorities and industrial scientists, resulting from their different outlook on toxicological problems: on the one hand we have the primarily or exclusively administrative official with a decidedly political position, on the other a scientific expert brought up on practical experimental problems and possessing high qualifications, perhaps even international renown. One way of resolving such misunderstandings and building up mutual confidence would be to remove the discussion of both fundamental and day-to-day problems from the province of officialdom into the scientific arena, as is the widespread practice in other countries. It is particularly desirable that toxicologists employed by the authorities should participate actively in scientific debates, their understanding of methodological problems being augmented wherever possible by their own practical contributions.

10. Minimum requirements should be stipulated for toxicity tests, although detailed rules as to procedures and evaluation entail some risk. Chronic experiments involving large numbers of animals of different species which receive doses in the vicinity of the threshold level usually proceed uneventfully. They yield great numbers of data relating to normal findings, and vigilance becomes blunted, so that if eventually an apparently slight—but decisive—change occurs, it tends to be overlooked. A decision as to whether importance should be attached to an effect that may not even rate statistical significance can only be reached properly after rapid and thorough consideration of all the experimental parameters, including molecular-biology relationships. Qualified scientists naturally shy away from the strict regimentation of chronic animal experiments and good trainees are hard to recruit. *Work in environmental toxicology should therefore be made more attractive.* The best way of achieving this is to do away with inflexible test procedures, such as have already become established in many fields, *e.g.* food additives, cosmetics, and drugs. Greater attention should be given to the more interesting clarification of the *mechanism of action* of foreign substances, an aspect that is neglected in current testing regulations. This would simultaneously raise the efficiency of the researcher, for study of mechanisms has contributed far more to our present knowledge of the relationships in environmental toxicological systems than has mere routine testing. In particular, emphasis should be placed on *fundamental research* and the *development of new methods* which will help us to obtain more meaningful results more quickly and at reduced cost. A principle of "more research, less testing" will help to recruit better candidates for an urgent task: conquest of the dark side of chemical progress.

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Quartz Crystals and Their Colors

By Gerhard Lehmann and Hans Ulrich Bambauer[*]

The many colors found in quartz crystals are always due to the presence of impurity atoms, whose concentrations rarely exceed 0.1 wt.%. The impurity atoms occupy either silicon sites in the lattice or interstitial sites in the channels parallel to the *c* axis of the quartz structure; very fine precipitations of foreign phases are sometimes also observed, though this is less common. In addition to intrinsic colors of transition metal ions, one also finds color centers produced by ionizing radiation. Regular distributions of impurity atoms and colors may develop in the crystals as a result of some factor connected with its growth. Most of the natural quartz colors, as well as others that do not occur in nature, have been produced in synthetic quartzes.

1. Introduction

Colored varieties of quartz crystals, which are colorless in the pure state, are of widespread occurrence, and have been valued from time immemorial as jewelry stones. This mineral was therefore classified in very early times on the basis of its color, and trivial names (Table 2) have been introduced to distinguish different types of quartzes. Attention was naturally given to the origin of the many colors. Apart from early, purely speculative interpretations, the first partial answers resulted from the determination of the trace contents and their correlation with the intensity of the colors, and often also from comparison with similar colors in glasses of known composition. Special mention should be made of the work carried out by *Holden*[1] and by *Wild et al.*[2] in the 1920's. It was possible to determine the trace element responsible for the color in most cases, but the structure of the lattice defects that give rise to the color[**] was still uncertain, since the experimental and theoretical principles required for their investigation had not yet been developed.

Decisive impetus was provided around the middle of this century above all by electron spin resonance and the ligand field theory. Assisted by other, mainly spectroscopic, methods of investigation, they led to the elucidation of the structure of the color centers in many minerals having no color of their own. At the same time, interest in color centers shifted from practical to scientific questions.

In general, the causes of color can be divided into three groups:

1. Ions of transition metals or rare earth metals that are incorporated in a state of atomic dispersion into the crystal structure, and cause selective absorption in the visible region of the spectrum because of their ligand field or electron transfer bands.

2. Electronic defects, which are preferentially formed at structural faults in crystals (impurities, vacancies or interstitial atoms) by ionizing radiation; by transfer of electrons, this always leads to complementary pairs of electron and hole centers. The assignment of absorption bands and other properties to one of these centers is usually difficult, and cannot be achieved by correlation of only two parameters. Electronic defects not associated with impurities are of minor importance with regard to the colors in quartzes; on the other hand, they form a large number of color centers in the alkali halides[3].

3. Heterogeneous inclusions, which can cause selective absorption and scattering of light; in many cases these simply produce turbidity in the crystals.

In the majority of cases, therefore, the color of quartzes is associated with the presence of foreign atoms.

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[**] The name "color centers" has been generally adopted for lattice defects of this type, even where they have no appreciable absorption in the visible region of the spectrum.

2. Crystal Structure of Quartz and Possibilities for the Incorporation of Trace Elements

The nature and amount of impurities that can be incorporated into a crystal under otherwise ideal conditions depend on the structure of the host and its dimensions.

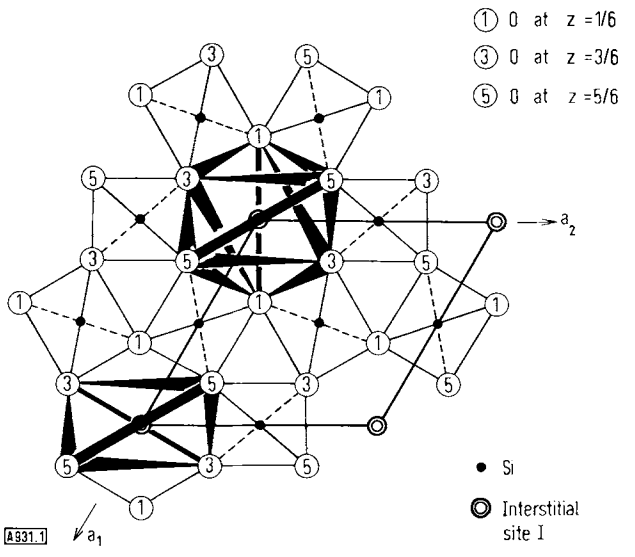

Fig. 1. Projection of the (average) crystal structure of high quartz on (0001). (The structure of low quartz differs from this only in small displacements of the parameters.) The two types of interstitial sites that occur in the channels parallel to the c axis, with distorted tetrahedral and distorted octahedral environments, are emphasized by the indication of spatial coordination in one example each: I_4 on $z = 4/6$ and I_6 on $z = 3/6$. After [38].

These in turn are determined by the nature and valency of the atoms from which it is formed. Figures 1 and 2 show the structural principle of quartz: $[SiO_4]^{4-}$ tetrahedra are linked by their corners to form three-dimensionally crosslinked Si—O—Si "chains", leaving relatively wide channels between the chains along the c and a axes of the unit cell. For clarity, the diagrams are based on the (average) high quartz structure (hexagonal point group D_6-622), which is stable above 573 °C. The structure of low quartz (trigonal point group D_3-32) differs from this only in small displacements of the parameters. In the channels along the (optical) c axis there are interstitial sites I_6 with distorted octahedral coordination and I_4 with distorted tetrahedral coordination, which are separated from one another by $c/6$. Si lattice sites occupied by foreign atoms will be denoted by S in the following discussion[*].

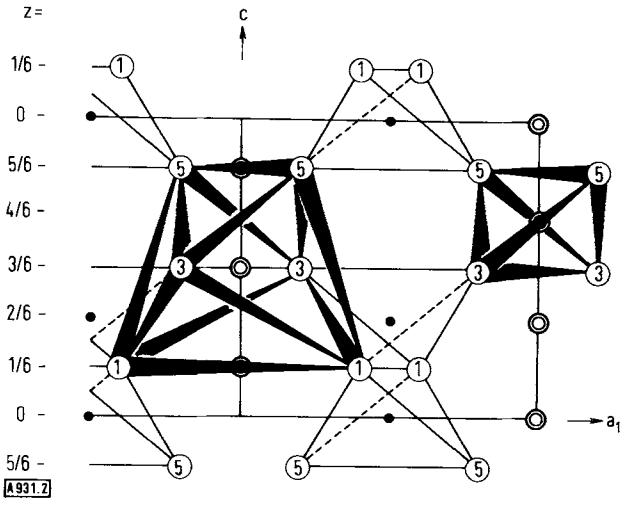

Fig. 2. Projection of the (average) crystal structure of high quartz on (01$\bar{1}$0); otherwise as in Figure 1. Only the interstitial sites I_6 are indicated in the channel parallel to the c axis on the left, and only the I_4 on the right. After [38].

Table 1 presents a survey of trace element contents in natural quartzes from recent literature data. These values can be illustrated with the aid of Figure 3. It should be noted that the upper limits indicated are extremely rare. One can see that the trace element content practically never exceeds 0.1%. Another interesting point is that elements forming tetrahedrally coordinated anions, such as S, P, and As, have not yet been found in natural quartzes, though the size of these complexes is such that they could replace $[SiO_4]^{4-}$ tetrahedra. That this is not entirely due to geochemical factors can be seen from the failure to incorporate these groups[23] or borates into synthetic quartzes. There must therefore be some kinetic inhibition that prevents the incorporation of negatively charged groups.

Table 1. Trace elements in natural quartzes. Table from [56] corrected according to more recent literature. The maximum values indicated are mostly rare, and values given in brackets are uncertain. Other elements are not indicated, either because their concentrations are too low, or because the number of analyses is too small or the analyses are uncertain.
The values are given a) in ppm (parts per million); b) as the number of atoms per 10^6 silicon atoms (often denoted by "ppm Si" in the literature).

		H	Li	Na	K	Al	Fe	Ti	Mn	Mg	Ca
Ordinary rock crystals and smoky quartzes	a)	< 1	0.2–12	< 1–8	< 5–20	3–65	< 1–16	< 1–10	< 1–10	< 1–4	n.d.
	b)	< 1–55	2–100	< 1–20	< 8–30	6–140	< 1–17	< 1–10	< 1–10	< 1–10	n.d.
Rock crystals with lamellar structure	a)	< 1–20	12–140	< 1–25	n.d.	90–1000	< 1–14	< 2–13	< 1–10	< 1–4	n.d.
	b)	35–1200	100–1200	< 1–60	n.d.	200–2300	< 1–15	< 2–13	< 1–10	< 1–10	n.d.
Amethysts and citrines	a)	< 1–15	< 1–35	5–75	3–35	5–350	10–300	< 1–5	< 1–60	5–120	4–450
	b)	< 1–1000 [a]	10–300	13–200	4–55	10–800	10–350	< 1–5	< 1–60	10–300	6–700
Rose quartzes	a)	n.d.	n.d.	(≈ 1000)	n.d.	(100–1000)	(25–3000)	30–400	1–70	10–300	30–100
	b)	n.d.	n.d.	(≈ 2500)	n.d.	(200–2000)	(25–3000)	40–500	1–70	25–750	45–150

[a] Assumed order of magnitude.

Substitution of the tetravalent silicon by other ions, particularly those of the transition and rare earth metals, is possible

[*] I from "interstitial", S from "substitutional".

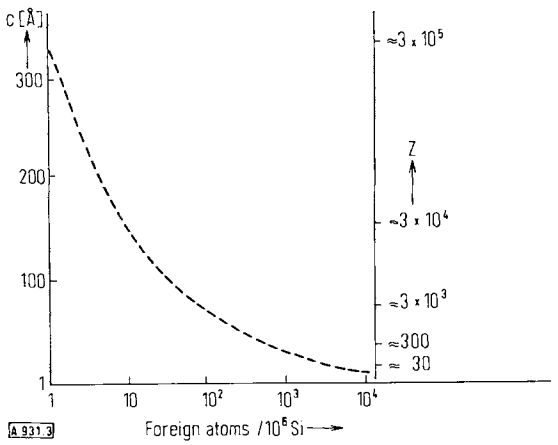

Fig. 3. Illustration of the concentration data for foreign atoms in Table 1. As values *averaged* over the analyzed range, Z is the number of unit cells and c is the edge length of the cube per foreign atom (which is also the shortest distance between two foreign atoms). (We are grateful to Prof. *Laves*, Zürich, for this diagram.)

only to a very limited extent, if at all, because of its high valency and its small ionic radius. This substitution has so far been observed for Al^{3+}[4], Fe^{3+}[5–7], Ti^{4+}[8], and Ge^{4+}[9–11]. One can understand, therefore, why quartz is one of the purest of all minerals. A series of additional ions have been found in interstitial sites: alkali metal ions, which can be replaced by one another or by hydrogen (or deuterium) by electrolysis or high-temperature diffusion[50], and the transition metal ions Co^{2+}, Co^{3+}[12], Fe^{2+}[7], Fe^{3+}[13], and almost certainly also Ti^{3+}[14]. The surprising ease with which the transition metal ions with higher valencies are incorporated into interstitial sites is evidently due to their d electrons[*]. Another influencing factor is the ligand field stabilization energy, as a result of which the octahedral coordination is energetically favored when the d shell is only partly filled, this effect being particularly strong in the case of Cr^{3+}. The almost exclusive incorporation of this ion into distorted octahedrally coordinated interstitial sites in $AlPO_4$[19] with a quartz superstructure[20] is a particularly striking example of this influence. It is possible to determine the coordination of this interstitial site (and the valency of the transition metal ion) from the optical spectrum on the basis of the ligand field theory.

Apart from the capacity of the quartz structure for the incorporation of ions, the incorporation of impurities is limited by their solubility in the hydrothermal growth solution and the partition coefficient between solution and crystal. At present there are few known quantitative data on either of these factors, in comparison with the large number of systems. It is occasionally found that the incorporation of one ion is strongly influenced by the presence of another. Thus distinctly more Co^{2+} is incorporated into synthetic quartz if the growth solution also contains beryllium salts[21]. It is also known that the incorporation of Al^{3+} is strongly favored if the solution contains alkali metal ions that can be incorporated. To dope synthetic quartzes with iron ions, it was necessary to use potassium carbonate solutions instead of sodium carbonate, since the sparingly soluble acmite $NaFe[Si_2O_6]$ is formed with Na^+[22]. In the case of the transition metals, which can exist in solution in various valency states, the redox equilibrium is shifted to the least soluble valency state. This explains the striking reducing action of alkaline hydrothermal solutions on transition metal ions[23], if one assumes that, contrary to the situation at room temperature, the solubility of the higher valency state increases with rising temperature, *e.g.* as a result of the formation of anionic complexes[14].

[*] It is well known that alkali metal halides exhibit Schottky defects, with vacancies in both sublattices, while the silver halides exhibit Frenkel defects, with vacancies and interstitial ions of Ag; similarly in the n conductor ZnO, the excess of zinc is achieved by the incorporation of additional Zn in interstitial sites, and not by vacancies in the oxygen sublattice. The factor responsible for the incorporation of metal ions into interstitial sites is the fact that the energy required is less than for the formation of vacancies in the anion sublattice. Thus the enthalpy of formation of the Frenkel defects in AgCl is only about 14 kcal/mol [15], whereas the enthalpy of formation of Schottky defects in alkali metal halides is around 23 kcal/mol or more [16—18].

3. Color-Producing Trace Elements

The colored varieties of quartz (cf. Table 2) can be classified from various points of view, the choice of which depends on the state of knowledge about the causes of color and the detection or synthesis of new varieties. Thus a differentiation based on the nature of the color or the mineralogical trivial name no longer seems appropriate, since several very different causes often produce similar colors, which are difficult to distinguish, and it would be necessary to introduce new trivial names for colors that have been obtained synthetically.

If there were no gaps in our knowledge of the structures of all color centers, these structures would form a suitable basis for differentiation. Our knowledge at present is adequate for a classification according to the nature of the color-producing trace element, and this is the basis that will be used here. It avoids the difficulty arising from the fact that the same crystal often contains different color centers in varying ratios, so that there may be doubt in a given case, from the mineralogical point of view, as to whether a crystal should be referred to as amethyst or as smoky quartz. On the other hand, further differentiation is necessary in cases where the same element produces different colors according to its valency, coordination, or degree of dispersion. This is particularly noticeable for iron.

3.1. Color Centers of Iron

This element was recognized at an early date as the source of the violet color of amethyst[1d, 2b]. The incomplete correlation between the iron content and the depth of color was also discovered in these investigations, but the reasons for this, as well as the nature of the color centers, remained unknown until very recently. The formation of the color centers by ionizing radiation and their low thermal stability point to an anomalous valency as their cause. ESR investigations[5, 24] showed the presence of trivalent iron in silicon sites of the lattice, with alkali metal ions in adjacent interstitial sites to compensate for the missing positive charge.

Table 2. Colored varieties of quartz.

Trivial name	Color	Color-producing trace element	Color center (scattering center)	Stability limit of color [°C]	Artificial preparation	Naturally occurring
Rock crystal	colorless	—	—	—	+	+
Smoky quartz	brown	Al	AlO_4^{4-} + electron center	*ca.* 200	+	+
	light yellow [a]	Al	AlO_4^{4-} + electron center	*ca.* 150	–	(+)
Amethyst	violet	Fe	$Fe^{4+}(S) + Fe^{2+}(I_4)$	*ca.* 350	+	+
Citrine	yellow-brown	Fe	Fe_2O_3-precipitations	*ca.* 600	–	+
—	yellow-brown	Fe	$Fe^{3+}(I_4)$	*ca.* 600	+	–
"Prasiolith"	green	Fe	$Fe^{2+}(I_6)$	*ca.* 600	+	(+)
Rose quartz	pink	Ti	$Ti^{3+}(I_6)$ (+ rutile needles)	*ca.* 575	–	+
Blue quartz	grey-blue	Ti	(rutile needles)	?	–	+
—	light-blue	Co	$Co^{2+}(I_4)$	?	+	–
—	red-brown	Co	$Co^{3+}(I_6)$	*ca.* 450	+	–

[a] Radiation color of certain rock crystals (see Section 3.4).

This S_1 center does not contribute to the color of amethyst itself, since the ligand field bands of trivalent iron have only a low intensity in the visible region of the spectrum, comparable with that in $AlPO_4$, $GaPO_4$, and $AlAsO_4$[25], and the first strong electron transfer band, as in $AlPO_4$ and $GaPO_4$, lies well above the visible region, with a maximum at 46000 cm^{-1} (see Fig. 4). Since the concentration of the S_1 centers increases on decoloration and decreases on discoloration, these must be regarded as precursors of the amethyst centers.

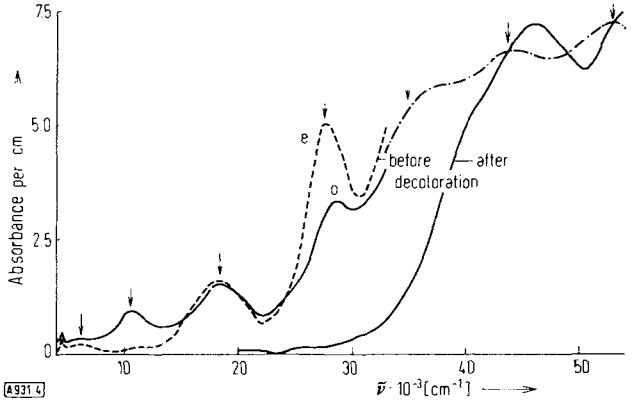

Fig. 4. Absorption spectra of amethyst (Four Peaks, Arizona) and their variation on thermal bleaching; o: light polarized perpendicular to the c axis (σ or o spectrum), e: light polarized parallel to the c axis (π or e spectrum).

A very similar center, but with a proton on one of the four oxygen ions of the $[FeO_4]^{5-}$ tetrahedron instead of the alkali metal ion in an interstitial site (S_2 center), is formed on discoloration as a by-product of the irradiation in concentrations that vary according to the hydrogen content of the quartz[7]. Its absorption in the visible and ultraviolet regions of the spectrum must be substantially similar to that of the S_1 center.

The first attempts at the hydrothermal synthesis of iron-doped quartzes led to a different incorporation of trivalent iron, as was shown by the completely different ESR spectrum of the centers, which were again atomically dispersed[26,27], and by the much higher optical absorption in the visible region, which leads to a pronounced yellow color in the crystals at concentrations of only about 0.01 at %. The analysis of this optical spectrum (Fig. 5) showed that the trivalent iron in this case is accommodated in inter-

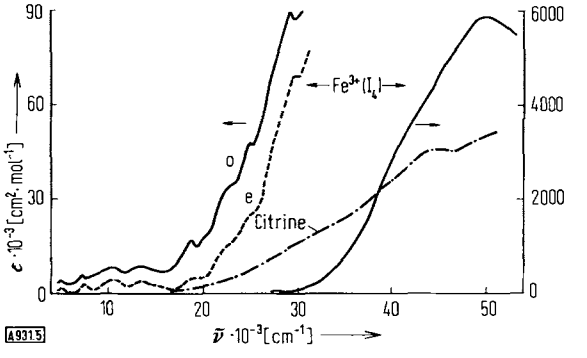

Fig. 5. Absorption spectra of yellow quartzes containing iron (arbitrary scale in the case of citrine).

stitial sites with approximately tetrahedral symmetry[13,28]. There are striking similarities between the optical spectra of this I_4 center and of the Fe^{3+} in alkali metal silicate glasses[29], in which Fe^{3+} also has a tetrahedral coordination as shown by Mössbauer investigations[30,31].

Analogies of this nature are also found for other transition metal ions, and transition metal ions in interstitial sites in the quartz structure generally have the same coordination as in silicate glasses rich in alkali metals[28]. The I_4 center is also found in bleached amethysts, but almost completely disappears on sufficiently long exposure to ionizing radiation if the concentration of S_1 centers predominates[27]. Conversely, in synthetic amethysts with more I_4 than S_1 centers, practically all the S_1 centers disappear on irradiation. An amethyst center thus consists of one S_1 and one I_4 center, which change their valency in opposite directions on irradiation. The depth of color attainable is therefore limited by the center that is present in the lower concentration, and if only I_4 centers are present (a situation so far found only in synthetic quartzes), irradiation does not lead to the formation of amethyst centers. The incomplete correlation between the iron content and the depth of color of amethyst can thus be explained as follows. Only in the ideal case of equal concentrations

of S_1 and I_4 centers and vanishingly small hydrogen contents (no conversion $S_1 \rightarrow S_2$) can all the Fe^{3+} be converted into amethyst centers, provided that the radiation dose is sufficiently high. The resulting model of the color centers as tetravalent iron in lattice sites and bivalent iron in interstitial sites[7][*] is supported by the optical spectra of amethysts (Fig. 4)[39]. Bands attributable to tetrahedral Fe^{2+} appear in the far UV and in the IR at 1600 nm, so that the color of the amethysts is due almost exclusively to the contribution of the Fe^{4+}. This explains the small variation of the colors of amethysts in comparison with other minerals colored by impurities[32]. The high intensity of the bands at 545 nm and shorter wavelengths[7] identifies them as transitions with charge transfer character in the sense of the MO theory, similar to the bands of the MnO_4^- and CrO_4^{2-} ions[34].

According to this model, crystals in which Fe^{3+} is incorporated exclusively in S_1 sites should also be incapable of discoloration to give amethyst, but such crystals have not so far been found as minerals or synthesized. The occasional occurrence of amethysts with abnormal properties (*e.g.* decoloration by daylight) indicates that other defects as well as the I_4 centers may act as electron acceptors.

By the use of suitably oriented crystal plates as seeds, partial incorporation of trivalent iron into S_1 sites has been achieved in sectors of the positive rhombohedron[22]. The synthesis of amethysts has thus been achieved in principle; however, the depth of color obtained is still low in comparison with that of natural amethysts, since a much greater proportion of the S_1 centers are converted into S_2 centers because of the high hydrogen concentration, and thus become unavailable for the formation of amethyst centers.

Strongly colored regions of natural amethysts turn brown when heated to about 500 °C; the color is very similar to that of natural citrines. Both give a broad isotropic ESR absorption at a g value of 2[7,33]. The lack of dependence of the line width on the microwave frequency[28] points to heterogeneous inclusions of Fe_2O_3, corresponding to the precipitation of $MnCl_2$ in alkali metal halides[35]. The optical spectrum of citrine is also isotropic (Fig. 5),

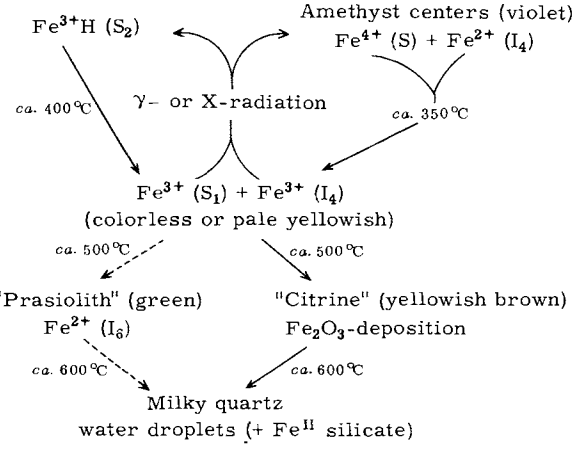

Fig. 6. Scheme of the observed changes in quartzes containing iron.

[*] The opposite arrangement is very unlikely for several reasons.

and its similarity to the absorption of Fe^{III} hydroxide sols was pointed out at an early date[1c].

Some amethysts turn green when heated to temperatures of about 500 °C; the optical spectrum[36] agrees with that of bivalent iron in I_6 interstitial sites in synthetic quartzes[7]. The cause of this thermal reduction is unknown. Temperatures around 600 °C produce a milky turbidity in amethysts, which is also known in other varieties of quartz, including synthetic quartzes with Z growth (cf. Section 4), where it has been traced to the separation of water droplets[37,58]. Milky quartz is occasionally also found in nature. It must also be assumed that under these conditions an Fe^{II} compound of unknown structure, probably an iron(II) silicate, is formed in amethysts and iron-doped synthetic quartzes[27].

The scheme in Figure 6 shows a survey of the possible transformations in amethysts. Because of the large number of reactions and migration processes that occur, this system is also of interest for kinetic measurements.

3.2. Cobalt

Doping with bivalent cobalt yields blue quartzes. The absorption spectrum (Fig. 7) practically agrees with that of Co^{2+} in silicate glasses that are rich in alkali metals[21]. It is typical of tetrahedral coordination of this ion, and can only be explained by incorporation in interstitial sites I_4[12], since occupation of the lattice sites (which are also tetrahedral) would cause a strong displacement of the bands to shorter wavelengths because of compression. Reddish-brown quartzes are obtained on doping with trivalent cobalt. Evaluation of the optical spectrum (Fig. 7) indicates that this ion occupies the interstitial site I_6[12].

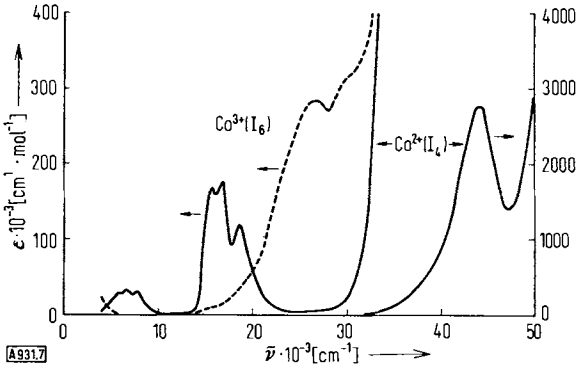

Fig. 7. Absorption spectra of synthetic quartzes doped with Co.

On heating to about 450 °C, the cobalt is reduced to the bivalent state, and this process is accompanied by a change of position from I_6 to I_4, as is shown by a comparison of the optical spectra. The activation energy for migration in the channels parallel to the c axis cannot therefore be very high, in agreement with the strongly preferred diffusion of monovalent cations along these channels[40]. On thermal reduction of Fe^{3+} to Fe^{2+} in the rare amethysts that can be turned green, a migration from I_4 to I_6 is observed (cf. Section 3.1). The occurrence of the migration

and its direction are determined purely by the preference for a certain coordination of the ion having the lower valency, which results from the differences in the ligand field stabilization energies. The reduction of the trivalent cobalt is reversible if the heating is carried out for only a short time, but becomes irreversible on prolonged heating; this is an indication of diffusion processes with participation of the oxygen formed during the reduction.

3.3. Titanium

This element is responsible for the color of rose quartz, which is found mainly in cloudy, compact pieces, and rarely in small, well-formed crystals. The pink color is due to a band at 20400 cm^{-1} (Fig. 8), is not changed by radiation, and is also thermally very stable. It can be explained only by trivalent titanium in interstitial sites I_6[14]. The surprising formation of the trivalent state, which is sensitive to oxidation, can be attributed to the reducing action of the growth solutions, which was mentioned earlier. A small proportion of the titanium is incorporated in the tetravalent state into silicon sites in the lattice; this can be reduced to the trivalent state by ionizing radiation[43]. The turbidity is, at least in part, due to precipitated rutile needles, which are up to 0.1 mm long and have a very uniform diameter of about 0.05 to 0.07 µm[41,42]. Attempts to grow rose quartz hydrothermally have so far been unsuccessful[44].

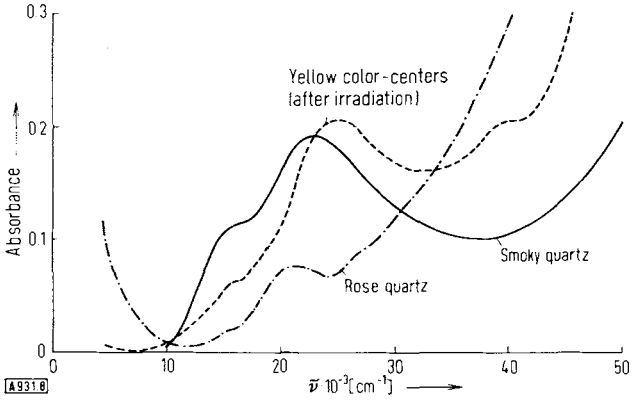

Fig. 8. Absorption spectra of quartzes with hole centers of aluminum and of rose quartz.

The gray-blue colored blue quartz also contains rutile needles, which are larger on average but less uniform than those in rose quartz[42].

3.4. Aluminum

Aluminum is the commonest impurity in natural quartz; Table 1 shows the range of variation found. Unlike the paramagnetic transition metal ions, this ion gives ESR and optical spectra that yield information on the manner in which it is incorporated only after the formation of electronic defects. The smoky quartz centers can be regarded as a defect electron on one of the four oxygen ions of substitutional $[AlO_4]^{5-}$ tetrahedra[4,46,47,53]; the elucidation of the structure was made possible by the hyperfine splitting of the ESR signal as a result of interaction with the nuclear spin of ^{27}Al. It is not yet known what becomes of the electron split off; *Mitchell* and *Paige* attribute absorption bands in the far UV to electrons in oxygen vacancies[48]. It seems quite possible that bands at longer wavelengths in smoky quartz (Fig. 8) are actually due to electron centers of this or of another kind, in analogy with the F centers in alkali metal halides and alkaline earth metal oxides[3,49]. The smoky quartz centers can be destroyed by UV radiation or by temperatures above 200 °C, and are thus less stable than amethyst centers.

In the region of Alpine deposits, the colorless quartzes (rock crystals) can be divided into two groups[51,56,59] according to trace element content (see Table 1) and macroscopic crystal defects[64]: 1. "ordinary rock crystals", with relatively low trace contents and a typical linear structure (Fig. 11) and 2. "lamellar quartzes", with relatively high trace contents and made up of a framework of low symmetry lamellas (Figs. 12 and 13)[57]. Natural smoky quartzes fit readily into the first group. Both groups are also found in deposits outside the Alps.

Most rock crystals assume a smoky quartz color under the action of ionizing radiation[56]. Much less common is a pale yellow color[22,50], which is thermally less stable than the smoky quartz color. The optical spectrum (Fig. 8) shows small band displacements compared to the spectrum of smoky quartz, and an additional band at 38500 cm^{-1}. Differences from smoky quartz are also found in the hydrogen content and in the ESR spectrum. The hydrogen content, with a value of *e.g.* about 10^2 H/10^6 Si, is distinctly higher than in typical smoky quartzes and near the lower limit of the values for "lamellar quartz". The content of other trace elements (Al, Li), in contrast with the "lamellar quartzes", appears to be no higher than in smoky quartzes and ordinary rock crystals. The ESR spectrum, as in the case of smoky quartz, shows the presence of holes on $[AlO_4]^{5-}$ groups. Irradiated "lamellar quartzes" frequently contain lamellar regions with a visually "normal" smoky color separated by regions with a brownish-yellow to yellowish color. This yellowish color could be the same as that mentioned above. No explanation has been found as yet for the differences between the corresponding color centers and the smoky quartz centers, and the assignment of the optical absorption bands to electron and hole centers has not yet been possible.

3.5. Color Centers Associated with Other Ions

The irradiation of germanium-doped quartzes leads to the formation of a series of electron centers with absorption bands in the near UV[52]. ESR studies[9,54,55] were again the principal aid to the elucidation of their structures.

New colors have been achieved by doping with other transition metal ions. The relationships to alkali metal silicate glasses that were mentioned earlier, in conjunction with the ligand field theory, allow a fairly reliable prediction of the coordination of a given ion and of the resulting color. Thus trivalent chromium is expected to be incorpo-

rated only in interstitial sites I_6, with production of a green color, as in $AlPO_4$[19]. However, the knowledge of such rules does not overcome the experimental difficulties associated with any attempt to dope with another foreign ion.

4. Non-Uniform Distributions of Impurities and Color Centers

It is extremely rare for the trace element concentration in quartz to be constant over the entire crystal. The anisotropy of the rate of growth and the kinetics of the deposition process (variations of temperature and concentration with time and with location) lead to sector and zonal structures in the real crystal.

a) *Natural Quartzes:* Their morphology is essentially described by the rhombohedron and the prism (Fig. 9). One finds mainly growth sectors of the positive rhombohedron $\{10\bar{1}1\}$, the negative rhombohedron $\{01\bar{1}1\}$, and the prism $\{10\bar{1}0\}$.

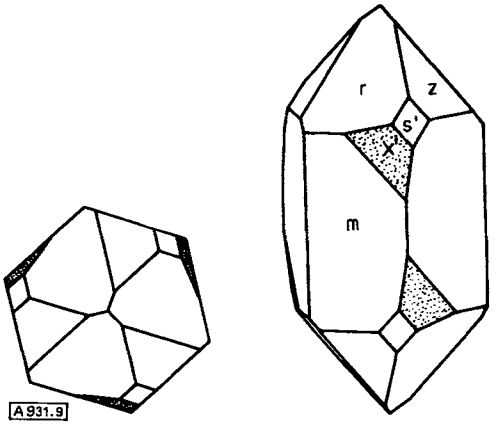

Fig. 9. Morphology of right-handed quartz; r = positive rhombohedron $\{10\bar{1}1\}$, z = negative rhombohedron $\{01\bar{1}1\}$, m = prism $\{10\bar{1}0\}$.

In the group of ordinary rock crystals and of smoky quartzes, the following relation is usually satisfied for the content of Al, Li, Na, and H: $r(10\bar{1}1) > z(01\bar{1}1) > m(10\bar{1}0)$[56]. Since the intensity of the smoky color due to irradiation is approximately proportional to the total content of trace elements, the sector

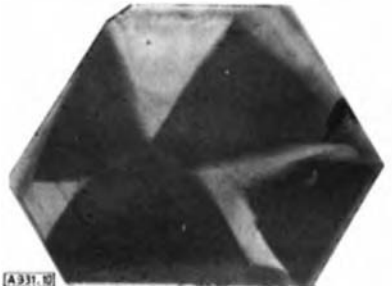

Fig. 10. Plate perpendicular to the *c* axis of originally light smoky quartz, diameter ≈ 3 cm. Sector structure appearing after γ irradiation: positive rhombohedron dark, negative rhombohedron light, outermost prism light. Dark region in the light sector on the right: Growth sector following positive rhombohedron in twinning position (Dauphiné law). Source: P. di Grandinagia, Swiss Alps [60].

Fig. 11. Plate parallel to the *c* axis of originally colorless "ordinary" rock crystal, approx. 3 cm wide. Visible after γ irradiation: zonal structure following positive rhombohedron (a roughly vertical Dauphiné twinning boundary runs through the middle of the section), as well as less strongly colored outer zones of the prism. The crystal defects characteristic of "ordinary quartzes" can be seen from the fan-like branching of the subindividuals. Source: Druckstollen Sta. Maria-Nalps, Swiss Alps [60].

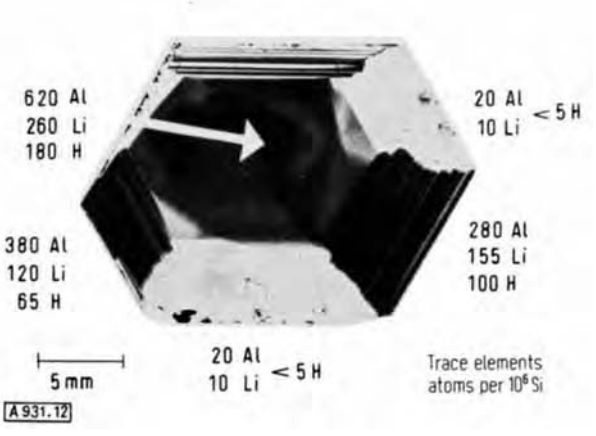

Fig. 12. Plate perpendicular to the *c* axis of originally colorless "lamellar quartz". After irradiation with neutrons: three outer sectors with radiation-colored lamellas alternating with optically homogeneous, practically undiscolored sectors: central part lamellated after the two rhombohedra. Source: Madagascar [57].

Fig. 13. Section parallel to the *c* axis of radiation-discolored "lamellar quartz" as in Fig. 11, 9 mm wide. Boundary line of the lamellas parallel to negative rhombohedron and parallel to prism (running vertically) with dovetailing [57].

and zonal structure is easily recognizable in irradiated crystals, as can be seen from the examples in Figures 10, 11, and 14. Unlike the color produced artificially by

radiation, the (natural) smoky color of smoky quartzes exhibits exactly the opposite relationship for the color shades[56]. The lamellar structure of lamellar quartzes is also clearly shown by the irradiation color (Figs. 12 and 13). Amethysts (like irradiated rock crystals) are most deeply colored in sectors following the positive rhombohedron $(10\bar{1}1)$.

Irregularity in the distribution of foreign atoms and color can also be caused by twinning and macroscopic imperfections, as is also clear from the examples in Figures 10 and 11.

b) *Synthetic Quartzes:* Synthetic quartzes generally also tend toward the morphology shown in Figure 9. An additional factor here, however, is the shape and orientation of the seed introduced, causing planes that do not normally occur in the crystal, such as (0001), to grow. This is illustrated in Figure 14 for a synthetic quartz grown from a rod-shaped seed (so-called Y bar), whose long edge is perpendicular to the prism face. A plate was cut from the crystal in the plane of the X and Z axes (the a and c crystallographic axes), *i.e.* parallel to the prism. Neither X or Z is a normal growth direction. The following relationships have been found for the enrichment of foreign atoms in various sectors in such crystals: $(0001) < (2\bar{1}\bar{1}0) < (11\bar{2}1) < (51\bar{6}1)$[63] and $(0001) < (10\bar{1}1)$[61]. The polar directions $+X$ and $-X$ differ not only in growth rate but also in capacity to accommodate impurities: $(0001) < (2\bar{1}\bar{1}0) < (\bar{2}110)$, *i.e.* more foreign atoms can be accommodated in direction $+X$[62]. The depth of the smoky color produced by radiation accordingly also increases. Correlations between impurities that are incorporated in different ways have been demonstrated in the zonal structure in the Z direction on a Z seed crystal[58].

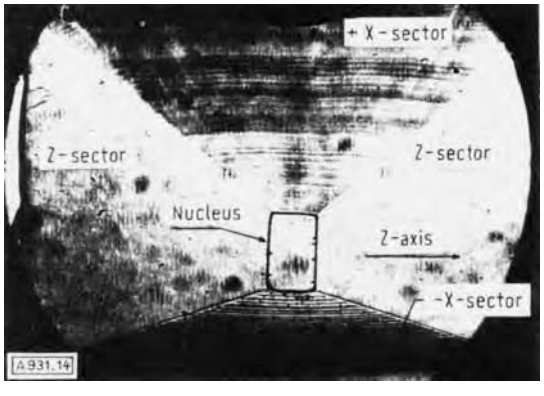

Fig. 14. Section parallel to the X—Z plane (a—c plane) through synthetic quartz (Y bar), γ-irradiated, approx. 2 cm wide. Growth sectors with zonal structure following Z and the polar directions $+X$ (rapid growth) and $-X$ (slow growth), hence eccentric position of the seed [45].

Another type of non-uniform distribution of color centers can be detected in certain amethysts. The Fe atoms substitute the three equivalent Si positions in the cell to very different extents. Amethysts of this type exhibit pleochroism in three mutually perpendicular directions (trichroism). Annealing at 600 °C leads to a random distribution of the centers, and after irradiation a dichroism corresponding to a trigonal symmetry is found[5].

An ordered distribution of foreign atoms (mainly Al, Li, H) has also been assumed to explain the nature of the similarly pleochroitic, smoke-colored lamellas in lamellar quartz after irradiation[57].

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Synthetic Precious Stones[**]

By Josef Liebertz[*]

The first industrially feasible process for the synthesis of rubies was developed by *Verneuil* around the turn of the century. Progress in growing single crystals led in time to numerous other processes, some of which can be applied to the production of precious stones. In this way it became possible to synthesize the most important precious stones. Even crystals that do not occur in nature, but were originally of interest in other connections, have acquired importance for jewelry in recent years.

1. Introduction

True precious stones are minerals that usually occur as crystals and are characterized by beauty of color, play of light, and brilliance. This visual impression is considerably enhanced by skillful cutting. A high degree of hardness is required to avoid wearing away during use; the hardness of most precious stones exceeds 7 (hardness of quartz) on the Mohs' scale, but it can also be as low as about 5, particularly for polycrystalline material such as lapis lazuli. In addition to the aesthetic factors, a precious stone must be rare, and therefore valuable. The values can easily be as high as, and even exceed, 10^5 DM/cm^3.

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Synthetic precious stones, on the other hand, are industrial products that agree crystallographically, physically, and chemically with the natural precious stones. The agreement almost self-evidently does not extend to the value, since the purpose of the synthesis is precisely to overcome the rarity. The favorable price of synthetic precious stones and the possibility of growing large crystals have opened up a wide field for technical use in addition to the use in jewelry.

The synthetic precious stones have the same names as the corresponding natural stones, preceded by "synthetic". It is accordingly incorrect, for example, to speak of a synthetic tourmaline. Really it would be a tourmaline-colored synthetic spinel. Some synthetic jewelry stones cannot be strictly referred to as precious stones, since no corresponding mineral exists. Compounds of this class were in most cases originally prepared for the sake of their physical properties, and their use for jewelry followed later.

With progress in growing single crystals, the number of processes for the production of synthetic precious stones has greatly increased. It therefore seems appropriate to present a survey of these processes first, and then to deal

with the particular precious stones and jewelry stones. Their principal properties are summarized in Table 1.

Table 1. Properties of precious stones and jewelry stones.

Crystal	Composition	Point group	Hardness (Mohs')	Refr. index	Dispersion	Growth process[a]
Diamond	C	m3m	10	2.42	0.04	Hp
Corundum (ruby, sapphire)	Al_2O_3	$\bar{3}$m	9	o 1.77 e 1.76	0.01	Ve, Cz, Fl, Hy *etc.*
Spinel	$MgAl_2O_4$	m3m	8	1.73	0.01	Ve, Cz, Fl
Beryl (emerald)	$Al_2Be_3Si_6O_{18}$	6/mmm	7.5–8	o 1.58 e 1.57	0.01	Fl, Hy
Quartz	SiO_2	32	7	o 1.54 e 1.55	0.01	Hy
Rutile	TiO_2	4/mmm	6–6.5	o 2.62 e 2.90	≈0.18	Ve
Strontium titanate (Fabulite)	$SrTiO_3$	m3m	6–6.5	2.41	0.10	Ve
Yttrium aluminum oxide (YAG)	$Y_3Al_5O_{12}$	m3m	8–8.5	1.83	0.03	Cz, Fl
Lithium niobate	$LiNbO_3$	3m	5–5.5	o 2.30 e 2.21	≈0.13	Cz

[a] Abbreviations: Hp = high-pressure method; Ve = Verneuil method; Cz = Czochralski method; Fl = flux method; and Hy = hydrothermal method.

2. Growing Methods

2.1. Verneuil Process

Around the turn of the century, *Verneuil*[1–4] developed the process that bears his name for growing rubies in the oxyhydrogen flame. The Verneuil synthesis may be regarded as a classic synthesis in that it was the first industrial method for growing precious stones, and is still used for the production of corundum, spinel, and other high-melting compounds. Its undiminished importance can be seen from the fact that the present annual world production is around 2000 tonnes of corundum and spinel.

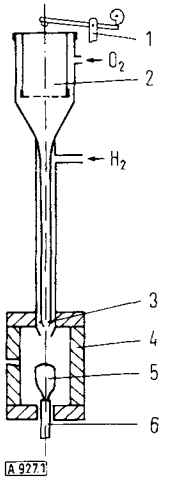

Fig. 1. Verneuil apparatus: 1, tapping apparatus; 2, powder container with perforated base; 3, burner jets; 4, ceramic muffle; 5, crystal; 6, sintered corundum crystal support.

The procedure of the Verneuil process can be seen from Figure 1. Hydrogen and oxygen are led through the outer and the inner tube respectively to the oxyhydrogen burner, whose jet is directed downward. The finely powdered starting material (<20 μm) is held in a container with a perforated base, and a tapper or vibrator is used to introduce it into the oxygen stream, and hence into the flame. A sintered corundum rod projects upward into the flame to act as the crystal support. Thermal insulation of the flame is provided by a ceramic muffle with a small peephole.

The flame temperature is initially adjusted so that the powder forms a sintered cone on the rod, and the tip of the cone is then fused. For nucleus selection a thin neck is first allowed to grow, and this rapidly widens to form the actual crystal as the supply of material and of gas is increased. The initial stage can be appreciably shortened by the use of a seed crystal. The top of the crystal is covered with a film of molten material up to 1 mm thick. The crystal holder is lowered at a rate of 5 to 10 mm/h, corresponding to the rate of growth, so that the position of the growing crystal surface in the flame remains constant. The gas consumption is about 1.2 m^3/h of H_2 and 0.4 m^3/h of O_2. For industrial production, about 50 units are combined to form a battery, and one man supervises three batteries.

The crystals produced in this way generally have a diameter of 10 to 20 mm and a length of 50 to 80 mm, though considerably greater dimensions are possible in special cases.

2.2. Czochralski Process

Whereas the Verneuil method was actually developed for the synthesis of precious stones, the Czochralski method[5] was originally used for the crystallization of metal filaments. It was introduced into semiconductor technology in a modified form; it is now one of the most important methods for growing crystals from the melt, and has a wide range of applications.

The principle of the method can be seen from Figure 2. The molten material from which the crystal is to be grown

is held in a crucible, which is usually induction heated by a high-frequency generator. This has the advantage that the maximum temperature attainable is limited only by the crucible material and the power of the generator. Platinum, rhodium, iridium, molybdenum, and tungsten are mainly used as crucible materials. The seed fixed in the base of the drawing shaft is in contact with the melt, and is brought to the desired diameter by adjustment of the temperature.

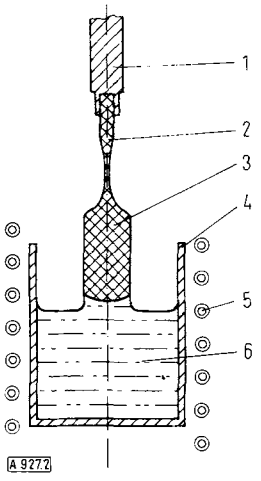

Fig. 2. Czochralski technique: 1, drawing shaft; 2, seed with tapered neck; 3, growing crystal; 4, crucible; 5, high-frequency inductance coil; 6, melt.

The temperature of the melt and the diameter of the crystal are then kept substantially constant. The crystal grows from the melt at a rate corresponding to the drawing rate, which can vary between 1 and 50 mm/h. The drawing shaft generally rotates at a rate of 30 to 150 rpm to keep the temperature and the distribution of impurities in the melt uniform and to reduce the diffusion boundary layer. The danger of constitutional supercooling can be avoided in this way.

The crystals produced by the Czochralski process are in the form of rods. Their diameters range up to about 50 mm, and their length up to about 1 m.

2.3. Flux Method

In the flux method, the desired compound is crystallized from a molten mixture consisting of the dissolved compound and the flux. The choice of the flux is naturally strongly dependent on the nature of the crystal to be grown; borates, molybdates, fluorides, and lead oxide have proved to be particularly suitable. The vessel is usually made of platinum. Depending on the system chosen, the temperature can be between 600 and 1300 °C. In the flux method, therefore, the crystals are grown from solution at high temperatures.

To produce the supersaturation required for crystallization, the initially slightly undersaturated melt is slowly cooled, possibly with a seed suspended in it; cooling rates of 0.1 to 1 °C/h are usual. The temperature difference principle described in Section 2.4 is occasionally also used for the crystallization.

Since growing times of several weeks must be expected and the size of the crystals is generally restricted to a few cm or less, the flux method cannot compete with melt methods. In general, it is used only if the crystal modification melts incongruently or undergoes a destructive phase transition in the solid state, so that the growing must be carried out below the temperature in question.

2.4. Hydrothermal Process

An alternative to the cases just mentioned is offered by the hydrothermal process, which is carried out between 300 and 600 °C, usually in the range above the critical temperature. Additives known as mineralizers are introduced into the water used as the solvent to increase the solubility. To ensure that the liquid or fluid solution phase has an adequate density of about 0.7 g/cm^3 (corresponding to 70% filling at room temperature) the *P-V-T* diagram of H_2O[6] shows that pressures between 200 and 3000 b are required in the temperature range mentioned. This means that the growing must be carried out in autoclaves. Because of the comparatively low solubility (<1%), only the temperature difference principle is used.

Figure 3 shows a diagram of the usual arrangement. The solution space, which is at a high temperature, is partly filled with lumps of feed material. A few seed crystals are suspended in the upper growth space at a lower temperature.

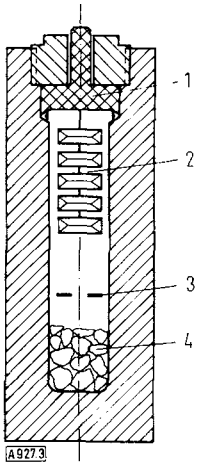

Fig. 3. Autoclave for hydrothermal growing: 1, self-sealing cover with delta ring; 2, growing space with crystals (T_0); 3, baffle; 4, solution space with feed material ($T_u > T_0$).

The saturated solution rises from the bottom, is supersaturated at the top, and thus supplies material to the growing crystals. To obtain favorable transport and flow conditions, a baffle is placed between the two regions.

Because of the serious corrosion problems, it is usually necessary to protect the autoclave *e.g.* with a silver or gold lining. Alternatively, the actual reaction vessel may be a sealed tube fitting loosely into the autoclave. To prevent the tube from breaking open, provision must be made for pressure equalization in the intervening volume.

3. Precious Stones

3.1. Diamond (C)

The name diamond is derived from the Greek word "adamas", which means the invincible. This refers primarily to the hardness of 10, but for a long time it might equally have referred to the synthesis, which was achieved only in 1955 at General Electric in the USA[7,8] and independently at ASEA in Sweden[9].

Direct transformation of graphite into diamond requires pressures of more than 120 kb at temperatures around 3500 °C[10]. The conditions for the catalytic synthesis are much more favorable, being 1500 to 2500 °C and 50 to 80 kb. The industrial production of diamond is therefore carried out only in this range, with transition metals as catalysts.

Several designs have been proposed and executed in order to realize the extreme pressure-temperature conditions in industry; the most important of these are the belt apparatus[10,11] and the tetrahedron apparatus[12]. (For further information see *e.g.*[13].)

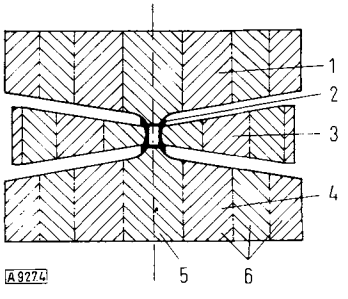

Fig. 4. *Hall*'s belt apparatus [10]: 1, upper ram; 2, sample chamber with pyrophyllite lining; 3, belt; 4, lower ram; 5, tungsten carbide; 6, various steels.

The belt apparatus (Fig. 4) is a modification of the ram-cylinder arrangement commonly used for lower pressures. The load is applied uniaxially with a press to the two rams, which taper very rapidly on the high-pressure side. The crucial feature is the lateral support ring (belt) surrounding the sample chamber. To even out mechanical stresses, the rams and the belt are made from several layers of material shrunk on to one another, with tungsten carbide inside and steel outside. The sample chamber is lined with the aluminum silicate pyrophyllite, which serves both as a pressure transfer medium and for electrical and thermal insulation. Since heating is carried out by direct passage of current, metal or graphite heating elements must be inserted in the pyrophyllite body. The operating times are usually less than 30 minutes, the pressure being increased first and then the temperature, whereas at the end of the operation, the pressure is released after cooling.

The tetrahedron apparatus consists of four rams in a tetrahedral arrangement, each of which is driven by its own hydraulic system. With a suitable conical arrangement of three rams and application of the pressure to the fourth, however, a normal high-pressure press can also be used for laboratory purposes[14]. Reference should also be made to an apparatus developed by a Japanese group[15], again on the basis of the multiaxial principle, with a hexahedral arrangement of rams; this apparatus has the advantage that it is self-adjusting.

The synthetic diamonds generally have dimensions of a few tenths of a millimeter and are therefore suitable only for industrial purposes at present. Nevertheless, about 40% of the industrial requirements are supplied by synthetic diamonds. The main producers are General Electric and De Beers. Diamonds that satisfy the size and quality criteria for jewelry stones are also produced in exceptional cases, but at a cost that could never be recovered. Thus 3/4 ct water-clear diamonds having the face combination (111)+(100) have been obtained at General Electric[16].

3.2. Corundum (Al_2O_3)

The industrial production of corundum crystals is still carried out almost exclusively by the Verneuil process, which was described in Section 2.1. The fine, free-running powder required as the starting material is obtained by calcination of ultrapure ammonium aluminum alum at about 1100 °C; it consists of a mixture of α-Al_2O_3 and Al_2O_3 transition phases.

For colored stones, the transition metal oxide used for doping is added to the alum in the form of the sulfate. Concentrations of between about 0.1 and 2%, based on the oxides, are usual. The most important additive is chromium oxide, which gives the red color of ruby, though Cr_2O_3 is itself green. This behavior, which seems surprising at first sight, is explained by the slight shift of the otherwise practically unchanged Cr^{3+} absorption spectrum toward shorter wavelengths in ruby[17]. The striking color change is thus primarily physiological in origin. A mixture of TiO_2 and Fe_2O_3 is used for the blue sapphire. Less important additives are NiO (yellow), Co_2O_3 (green), CoO (blue), and V_2O_3 (alexandrite-colored).

Linde[18,19] have been producing star rubies and star sapphires since 1947, and the production of these stones was later also started by Wiedes Carbidwerk[20,21]. A small quantity (about 0.3%) of TiO_2 is added to the starting powder, and dissolves in the corundum lattice at the high growing temperature. Prolonged annealing of the crystals in an oxidizing atmosphere between 1100 and 1500 °C leads to supersaturation with TiO_2; thin, oriented needles of rutile separate out, and these cause the asterism.

Only a small proportion of the synthetic corundums are intended for the jewelry industry, in which mainly colored crystals are used. The crystals for industrial use, on the other hand, are mostly colorless, apart from laser rubies and the traditionally red bearing stones for watches. Because of their excellent mechanical and thermal properties, synthetic corundums are used mainly as bearings and knife edges for instruments, pickup styli, thread guides in the textile industry, high-stress optical windows, mortars, and recently scratch-resistant watch "glasses" and substrates for semiconductor components.

In the case of ruby crystals, the quality and size requirements are frequently higher for industrial purposes. Thus

for laser rubies[22], a very homogeneous distribution of the Cr ions (concentration approx. 0.05%) is required. Moreover, with lengths of up to about 300 mm, these crystals must contain few dislocations, be free from mechanical stresses and scattering centers, and be strictly oriented (0°, 60°, or 90° between the *c* axis and the rod axis). The required uniformity of growth is achieved in particular by automation of the Verneuil process[23,24]. Shapes different from the usual boule or rod shape can be produced by appropriate movement of the seed crystal. With a crystal rotating perpendicular to the axis of the flame, one obtains circular disks (diameter about 80 mm), while eccentric rotation of the crystal gives tubes[25–28].

The Verneuil industry is concentrated mainly in Europe, apart from Linde (Union Carbide) in the USA, where production was started in 1940 because of the war. Important manufacturers include Djevahirdjian, Sadem, and Swiss Jewel Co. in Switzerland, Baikowski and Rubis synth. des Alpes in France, and Wiedes Carbidwerk in the German Federal Republic.

Attempts have also been made to grow corundum by other methods. Special mention should be made of the Czochralski process, which was described in Section 2.2, and which, at best, may offer an economical alternative to the Verneuil process. On grounds of cost, however, it is confined at present to laser rubies, which are produced by several firms and laboratories[29–32] with good results.

The EFG (edge-defined, film-fed growth) process, which was recently developed by *LaBelle et al.*[33–35], and which is partly based on the Czochralski principle, seems very promising. An important feature of this method is a molybdenum tool situated in the Al_2O_3 melt, the top edge of the tool projecting above the surface of the melt in the crucible, but still being covered with a film of melt because of the surface tension. This film is continuously replaced during crystallization, which takes place immediately above it, so that the growth front always remains in the same place. Figure 5 illustrates the arrangement for a tube. The shape

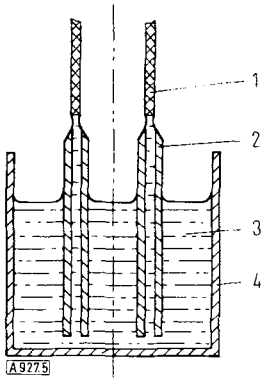

Fig. 5. EFG process after *LaBelle et al.* [33–35] for growing profiled single crystals, *e.g.* tubes: 1, tubular corundum crystal; 2, molybdenum tool; 3, Al_2O_3 melt; 4, molybdenum crucible.

of the crystal is determined by the design of the tool, and in addition to filaments, rods, and strips, single crystals with practically any desired profile can be produced from usually colorless corundum by the EFG process, examples being square tubes or tubes with several bores. The lengths reached are up to 115 m in the case of filaments and 150 cm for other profiles, the latter having transverse dimensions of up to 25 mm. The growth rates are surprisingly high, and exceed the values normally found in the Czochralski process by a factor of more than 100; they are between 2.5 and 5 cm/min, and even up to 20 cm/min for crystals oriented along the *c* axis.

Another process for growing corundum from the melt[36] is reminiscent of *Stöber*'s method[37]. The aluminum oxide is melted in a vacuum furnace with a graphite heating element (Tammann furnace). The crucible, which is made of molybdenum, is cooled at the center of the base by an adjustable stream of helium gas. The crystallization begins here and proceeds toward the wall of the crucible and upward. The monocrystalline growth can be reinforced by the use of a seed. The largest disk-shaped crystal obtained in this way has a diameter of 150 mm and a thickness of 68 mm.

The last method to be mentioned for growth from the melt is vertical zone melting, which is of limited interest in connection with laser rubies. The zone can be melted by the focused light of CO_2 lasers[38], arc lamps[39], or xenon lamps[40]. The crystals are considerably smaller than the rods produced by the Verneuil and Czochralski processes.

The natural genesis conditions are most closely approached in growth from fluxes or hydrothermal growth. Crystals obtained in this way are always idiomorphic, and are more difficult to distinguish from natural crystals. Because of the disadvantages mentioned earlier, however, these methods are of little importance for the production of corundum, which is easy to grow from a melt. It is reported that Chatham in San Francisco is to market rubies crystallized from fluxes that are of outstanding quality for jewelry. Mixtures of PbO, PbF_2, and B_2O_3 have proved suitable as fluxes[41–43]. The temperature range for growing extends from 1250 to 950 °C, and the cooling rate is about 1 °C/h. The hydrothermal synthesis of corundum[44,45] is best carried out in 1 M to 2 M K_2CO_3 or Na_2CO_3 solutions between 400 and 500 °C, and has led to crystals measuring up to 60 mm.

3.3. Spinel ($MgAl_2O_4$)

The industrial synthesis of spinel is carried out exclusively by the Verneuil process[46], the production conditions being almost the same as for corundum. Since the spinel with the stoichiometric composition presents great difficulties, a molar ratio of Al_2O_3:MgO greater than 1, and generally equal to 3.5, is always used to facilitate growth. An excess spinel of this type may be formally regarded as a solid solution of $MgAl_2O_4$ and γ-Al_2O_3, which also crystallizes in the spinel lattice. The powder is prepared from ammonium aluminum alum and magnesium sulfate. The spinel boules often have an approximately square cross-section, whereas the corundum pears are rarely polygonal.

Since jewelry is by far the predominant use of synthetic spinels, the color is important. The current aim is to simulate the colors of precious stones that cannot yet be

synthesized, such as aquamarine and tourmaline. As in the case of corundum, the crystals are doped with bivalent and trivalent ions of the transition metals, which can occupy tetrahedral magnesium sites or octahedral aluminum sites in the spinel lattice. An interesting phenomenon is the incorporation of Cr^{3+}[17], which produces the visual color red in the stoichiometric spinel, but leads in stages to pure green in the excess spinel beyond a molar ratio of 3. Thus the natural (stoichiometric) spinel containing chromium is red, whereas the usual synthetic spinel containing chromium is the same green as Brazilian tourmaline.

Spinel has also been successfully grown in the laboratory by the Czochralski method[47] and from PbO/PbF_2 mixed melts[41]; crystals having the stoichiometric composition can be obtained in this way.

3.4. Beryl ($Al_2Be_3Si_6O_{18}$)

The synthesis of beryl, for understandable reasons, is applied mainly to the most valuable variety, the chromium-containing emerald. According to general experience, beryl melts incongruently at about 1475 °C, and on slow cooling, it does not form a melt having the same composition even as a subsidiary phase[48]. The synthesis of beryl from the melt mentioned by *Gentile et al.*[49] and *Wilson*[50] is therefore extremely doubtful. The only growing methods worth considering are the methods based on crystallization from solution (Sections 2.3 and 2.4).

Large emerald crystals measuring up to 30 mm were first grown at the former I. G. Farbenindustrie, and were called Igmeralds. Production was stopped in 1942 because of the war. The process is based on the diffusion of the oxide components into a lithium molybdate melt with reaction to form beryl; BeO and Al_2O_3 are situated at the base of the crucible, and SiO_2 glass floats on the melt[51]. Of the present-day producers, Chatham (San Francisco), Gilson (Pas de Calais), and presumably also Zerfass (Idar-Oberstein) also use melts containing fluxes, as can be deduced from comparative investigations[52]. Their precise growing conditions are kept secret. The literature[52-55] contains reports of numerous fluxes, among which the systems Li_2O-MoO_3, Li_2O-WO_3, and PbO-V_2O_5 appear to be particularly suitable. The temperature range extends from about 700 to 1200 °C. The crystallization is carried out either by slow cooling or by transport in a temperature gradient.

It is only in the last few years that good results have been obtained in the hydrothermal synthesis of emerald. *Lechleitner* (Innsbruck) first confined his attention to the application of strongly colored epitactic emerald layers to previously polished, pale natural beryls, but since 1962 he has also been producing completely synthetic emeralds. Linde[52,56] also uses the hydrothermal process, with temperatures of 500 to 600 °C and pressures of 1000 to 1500 b. NH_4Cl is very effective as a mineralizer in concentrations of up to 11 mol/l. In another publication[57], 5% solutions of H_3BO_3 or $Na_2B_4O_7$ are reported to be advantageous. The pressure and temperature conditions correspond to those mentioned above.

3.5. Quartz (SiO_2)

Apart from the varieties amethyst, citrine, and smoky quartz, quartz finds very little use as a precious stone. On the other hand, colorless quartz is of great industrial importance for piezoelectric applications, particularly as resonators. About one third of the requirement for this purpose is currently supplied by synthetic crystals.

Because of the phase transition to β-quartz at 575 °C, the growing of quartz must be carried out below this temperature; the only method that can be used is therefore the hydrothermal method, which can now be carried out industrially[58-61]. Autoclaves up to 3 m high (capacity about 500 l) are used. The temperature is about 400 °C, the packing is about 85%, and the pressure is therefore about 1500 b. 1 N NaOH or Na_2CO_3 is used as the mineralizer. Since the growth rate is greatest in the direction of the *c* axis, basal plates are generally used as seed crystals. In this way, 40 crystals weighing more than 1 kg each can be grown in one autoclave within three weeks. The synthetic quartz crystals offer important advantages in preparation, since they are always untwinned and of uniform shape and size, so that the examination and orientation required for natural material is unnecessary.

Colored quartzes can be grown hydrothermally with suitable doping, particularly with cobalt (blue)[62,63] and iron (amethyst, green, yellow)[64-66], but little use has so far been made of these in the jewelry industry.

4. Jewelry Stones

4.1. Rutile (TiO_2)

Natural rutile crystals are always dark because of the presence of impurities, and are therefore unsuitable for use in jewelry. However, pure TiO_2 crystals were grown by the Verneuil process in 1948 at the National Lead Co.[67] and Linde. Though the flame is operated with an excess of oxygen, *e.g.* by an additional external supply of O_2 in a tricone burner[68], the crystals obtained are black because of a deficiency of oxygen. On subsequent annealing at lower temperatures in oxygen, however, they become almost colorless, with a very light yellow hue.

The fact that synthetic rutile has a higher refractive index and dispersion than diamond suggests its use as a substitute for diamond. On the other hand, the resulting play of color is so striking that large cut stones look artificial or even trashy. Moreover, the edges of the facets look washed-out because of the high birefringence.

4.2. Strontium Titanate ($SrTiO_3$)

Strontium titanate, which is structurally a perovskite, is even more favorable than rutile for the replacement or simulation of diamond. It is completely colorless and optically isotropic, and its refractive index agrees very closely with that of diamond; only the dispersion is too high. Like

rutile, however, the hardness (approx. 6) leaves something to be desired.

Strontium titanate is grown by the Verneuil process, and as in the case of rutile, the oxygen deficit must be made up by subsequent annealing in oxygen[69]. The only manufacturer is the National Lead Co., which markets the $SrTiO_3$ crystals under the name Fabulite.

4.3. Yttrium Aluminum Oxide ($Y_3Al_5O_{12}$)

Yttrium aluminum oxide, whose formula is $Y_3Al_5O_{12}$, has the garnet structure, and is therefore often referred to as YAG (yttrium aluminum garnet). $Y_3Al_5O_{12}$ is derived from normal garnet $M^{II}_3Al_2Si_3O_{12}$ by coupled replacement of the bivalent cation by yttrium and of the silicon by aluminum, the yttrium occupying dodecahedral sites and the aluminum octahedral and tetrahedral sites. (For further information on the crystal chemistry of garnets, see [70].)

YAG was first used in industry. Crystals doped with lanthanides, particularly with neodymium, are suitable for lasers in continuous operation[71]. Because of isomorphism, YAG crystals can also be used as substrates for ferrimagnetic garnets of the type $Y_3Fe_5O_{12}$. Even better is $Gd_3Ga_5O_{12}$, whose lattice constants are the same as those of $Y_3Fe_5O_{12}$[72].

Now that economical growth is possible by the Czochralski process, yttrium aluminum garnet is also used in jewelry applications, where its relatively high hardness of about 8.5 is advantageous. Though the refractive index is not very high, YAG has been offered by Linde in recent years as a substitute for diamond. Colored crystals can be obtained by the incorporation of lanthanide ions into yttrium sites or of transition metal ions into aluminum sites.

The best growing method is the Czochralski method[31,72-74], but growing from fluxes[75,76] is also possible. The conditions are similar to those for growing corundum in both cases.

4.4. Lithium Niobate ($LiNbO_3$)

Lithium niobate is of interest mainly because of its ferroelectric and optical properties[77]. However, its high refractive index and strong dispersion suggests that it might also be used as a jewelry stone, though its hardness (5–5.5) is not entirely satisfactory. $LiNbO_3$ crystals are grown exclusively by the Czochralski technique. Very attractive colors can be obtained by the addition of oxides of the transition metals, particularly Cr_2O_3 (green), Fe_2O_3 (red), and CoO (blue)[78].

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Direct Quantitative Photometry on Thin Layer Chromatograms

By Ute Hezel[*]

The principal methods for the direct photometric evaluation of thin layer chromatograms are discussed with the aid of examples. Since light is strongly scattered by TLC adsorbents, absorption measurements in reflection are preferable to transmission measurements. In the reflection measurements, an approximation method for the Kubelka-Munk function leads to satisfactory straight calibration lines. The working range for quantitative reflection measurements is in the µg range, and the detection limit is of the order of 10^{-8} g. The standard deviation for spots of equal concentration is less than $\pm 1\%$. The signal-to-background ratio is improved by simultaneous measurement of reflection and transmission. The measurement of diminution in fluorescence ("fluorescence quenching") is found to be less sensitive than the reflection at the absorption maximum. However, combined measurement of the reflection and the diminution of fluorescence gives an increase in sensitivity as compared to pure reflection measurements. As in solution photometry, fluorescence measurements are generally much more sensitive than absorption measurements. The working range is normally in the ng region, and the detection limit is around 10^{-11} g. All the investigations described in this paper were carried out on the Zeiss chromatogram spectrophotometer.

1. Introduction

Since the development of thin layer chromatography (TLC) into a microseparation method that is widely used in all fields of chemistry, there has been a growing need for a quantitative investigation of TLC spots. Purely visual, subjective comparison of the spots, whether according to intensity of color or fluorescence intensity[1-4] or simply according to spot size[5], gives only an accuracy of at best 10—20%. A possible objective method is to scrape the individual spots from the plate, elute the substances from the stationary phase, and determine them by absorption photometry or fluorimetry. An accuracy of about 3% can be achieved by this method[6]. It has the disadvantage, however, that about 50—100 µg of substance per spot must be applied in order to attain a normal sensitivity and this accuracy; with quantities as large as these, the plate is often supersaturated, and one obtains badly separated, tailed spots. Moreover, the scraping and elution are time-consuming and subject to interference, and cannot be carried out accurately for overlapping spots[7]. These difficulties can be avoided if the spots are evaluated on the plate itself by absorption photometry or fluorimetry; one then speaks of "*in situ*" measurements[8-13].

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2. Absorption Measurements in Incident Light (Reflection)

TLC spots appear colored because they absorb a certain characteristic range of wavelengths from the incident polychromatic visible light. Less light is therefore reflected than from the white, non-absorbing background. This decrease in reflection as a result of absorption in the visible and also in the UV region can be used for the quantitative evaluation of the TLC spots. The relation between the degree of reflection and the concentration is not linear, but is best described by the Kubelka-Munk function[14-17]:

$$\frac{(1-R_{abs})^2}{2R_{abs}} = \frac{\varepsilon \cdot c}{s} = \frac{k}{s}$$

R_{abs} = absolute reflection
ε = extinction coefficient
c = concentration
s = scattering coefficient
k = absorption coefficient

For reflection measurements of this kind, the theory demands a uniform distribution of the sample within the measuring area. To satisfy this condition for measurements on TLC spots (here the concentration is greatest in the center), one can use a small measuring area (*e.g.* 1 mm²) in relation to the spot size. The total quantity of substance in a spot is then found by moving the spot in a meandering fashion over the measuring area. Care must be taken to ensure that each part of the spot is actually measured exactly once, *i.e.* that no part is measured twice or not measured at all. After this scanning operation, the experimental values are converted into Kubelka-Munk values and added. This gives a satisfactory straight calibration line, as shown in Figure 1, curve 1, for 0.1—2.0 µg of Sudan Red.

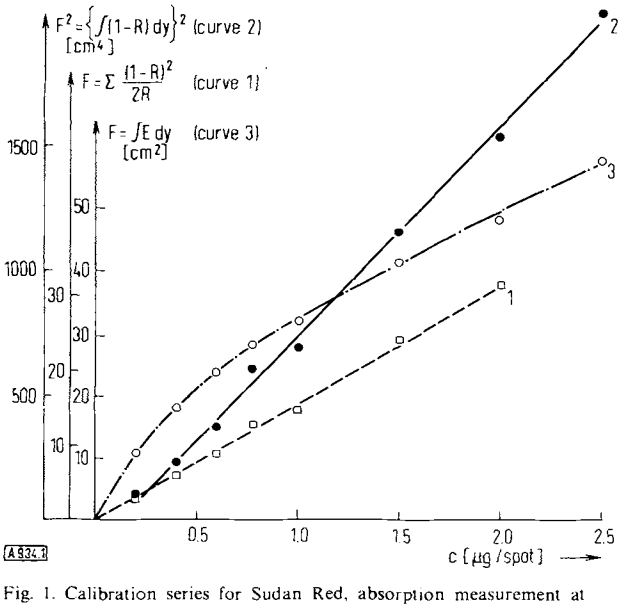

Fig. 1. Calibration series for Sudan Red, absorption measurement at $\lambda = 500$ nm.
Curve 1: reflection, point measurement and evaluation by means of the Kubelka-Munk function; curve 2: reflection, scanning with measuring slit and evaluation with the square of the area; curve 3: transmission, scanning with measuring slit and evaluation with the area in extinction units.

However, this method is very time-consuming, and efforts were therefore made to find a simplification that could be used in practice. If the TLC spots are scanned with a measuring area in the shape of a slit whose width is adjusted to correspond to the dimensions of the spot, one obtains *e.g.* the curve shown in Figure 2 for the reflection as a function of position. The square of the area between this curve and the baseline is plotted *versus* the concentration. Good straight calibration lines can be obtained in this way in the µg range (*e.g.* Fig. 1, curve 2)[18-23]. The concentration range for which this approximation is valid is perfectly adequate in practice, and generally covers approximately one power of ten. We thus have a method whose deviations from linearity (correlation coefficients generally >99.5%) are smaller than the fluctuations due to plotting and to the chromatographic parameters. The overall error of the method is reported to be 3—4%[24]. The area between the reflection-location curve and the baseline can be closely approximated in most cases by a triangle. As can be seen in Figure 2, this graphic integration is reasonable even if the baseline is sloping. Correction for the reflection background, which varies slightly from spot to spot, can also be easily made by normalization of the interpolated average reflection background R_u at the spot to 100% reflection:

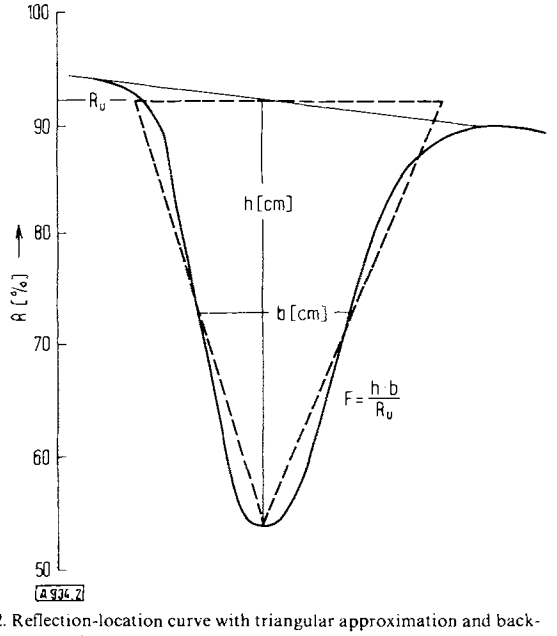

Fig. 2. Reflection-location curve with triangular approximation and background correction.

$$\text{Area } (F) = \frac{\text{Height } (h) \cdot \text{half band width } (b)}{\text{Average reflection background } (R_u)}$$

An important point here is that unlike in the double-beam method discussed below, the interpolated reflection background at the spot itself is taken into account. It has therefore been possible to achieve a standard deviation of 0.8% for the single value by this method (Table 1).

To eliminate background fluctuations, attempts have been made to apply the double-beam measuring principle, which is recommended in solution photometry, to measurements

Table 1. Reproducibility of eight Sudan Red spots containing 2 μg each on Merck commercial silica gel plates, solvent: benzene, measuring wavelength 500 nm.

h [mm]	b [mm]	R_u [%]	$F=\frac{h \cdot b}{R}$ [mm²]
107	36.5	94.5	41.3
107	36.5	94.5	41.3
107	36.5	93.5	41.8
108	36.5	94.5	41.7
107.5	36.5	94.5	41.5
105.5	36.5	93	41.4
106	36.5	93.5	41.4
104	36.5	93	40.8
		mean value	41.4
	standard deviation of single value		0.3 ≙ 0.73%
	standard deviation of mean value		0.1 ≙ 0.25%

on TLC plates[25-27]. However, this is effective only if the background in the track of the spot is identical with that in the reference track. This requirement is not satisfied in particular at the edge of the plate; differences of the order of 2 to 3% are not unusual. Such differences appear in full in the experimental value as systematic errors, and adversely affect the reproducibility in comparison with that of single-beam measurements. Moreover, the measuring track and the reference track must be separated from each other by lengthwise grooves in the separation direction. This is to prevent the TLC spots from diffusing into the reference track at higher R_f values. The result is a substantial change in the chromatographic conditions. In the first place, the spots become elongated, and the effectiveness of the separation thus deteriorates; secondly, unsymmetrical and dumb-bell shaped spots readily appear, probably as a result of interference with evaporation by the grooves, and the reproducibility and effectiveness of separation are further decreased. Moreover, the need for additional reference tracks reduces the sample capacity per plate.

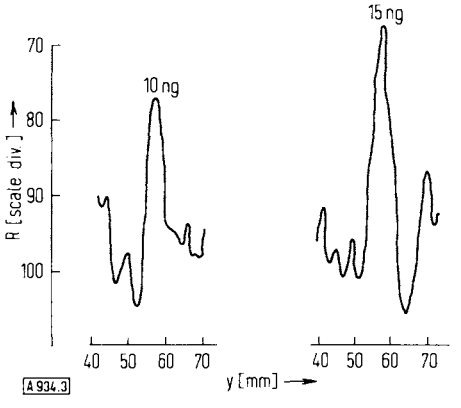

Fig. 3. Detection limit for caffeine on Merck commercial silica gel plates (without fluorescence indicator). Solvent: benzene/ether/glacial acetic acid (40:50:10); height of ascent 10 cm; reflection measurement, $\lambda = 275$ nm, measuring area 2×3.5 mm².

With single-beam reflection measurements, for example, 10 ng of caffeine can be detected directly at $\lambda = 275$ nm (Fig. 3). The signal corresponds to a change in reflection from 100% to approximately 99%. This small effect can be missed in the double-beam method because of the differences in the measuring and reference beams, which are of the same order of magnitude.

3. Absorption Measurements in Transmitted Light

It seemed reasonable to suppose that the transmission method commonly used in solution photometry should also be suitable for use, preferably in a double-beam arrangement, for the quantitative evaluation of TLC plates[25-27]. Unlike true solutions, however, TLC plates are strongly scattering media, for which the Beer-Lambert law is not obeyed. Figure 1, curve 3, shows clearly, for the case of Sudan Red, that the extinction-concentration line is strongly curved, particularly in the low concentration range; it can be approximated by straight lines only over narrow concentration ranges, and since these lines do not pass through the origin, they do not reproduce the linear relation between the extinction E and the concentration c that one would expect if the Beer-Lambert law were valid ($E = \varepsilon \cdot c \cdot d$). An approximation formula that straightens this curvature can be deduced from the Kubelka-Munk theory[27]. However, the empirically determined correction parameters are valid only for silica gel of a given quality, and are therefore not universally applicable. Reflection measurements with evaluation of the square of the area, on the other hand, give a satisfactory straight calibration line in the same concentration range (Fig. 1, curve 2). Above all, however, transmission measurements on TLC plates are possible only in the visible region, since most of the support materials used, such as glass or aluminum foil, completely absorb the measuring light in the UV, and since the layer itself has a considerable UV absorption, particularly in the short-wave UV range.

A further argument in favor of reflection measurements is provided by comparison of the signal-to-background ratios for measurements in reflection and in transmission. Faults in the plate, such as differences in grain size and in layer thickness, lead to greater background fluctuation in transmission measurements than in reflection measurements[7] (Fig. 4). Moreover, the evaporation of the solvent from the surface of the TLC plate during development leads to a flow of solvent, which pushes the spot against the surface[28] (Fig. 5). Reflection occurs almost exclusively on the surface layer, so that the relative concentration of the substance in the measuring area is greater than in transmission measurements, in which the total thickness of the adsorbent layer is included in the measurement. This is why the measured signal in transmission measurements is only insignificantly stronger than in reflection measurements, contrary to theoretical expectations[25,27]. Because of the lower background deviations, reflection measurements always give a better signal-to-background ratio than transmission measurements. It can be seen from Figure 6 that *e.g.* for Butter Yellow at $\lambda = 440$ nm on commercial silica gel plates, the signal-to-background ratio in reflection is better by a factor of 1.7 than in transmission.

Because of the strong background fluctuation in transmission measurements, a background correction is a pressing need. The double-beam method is of little value in this respect, since the background fluctuations in the paths of the measuring beam and of the reference beam are by no means identical. With a difference of *e.g.* 2% (which is quite possible) in the transmission background between

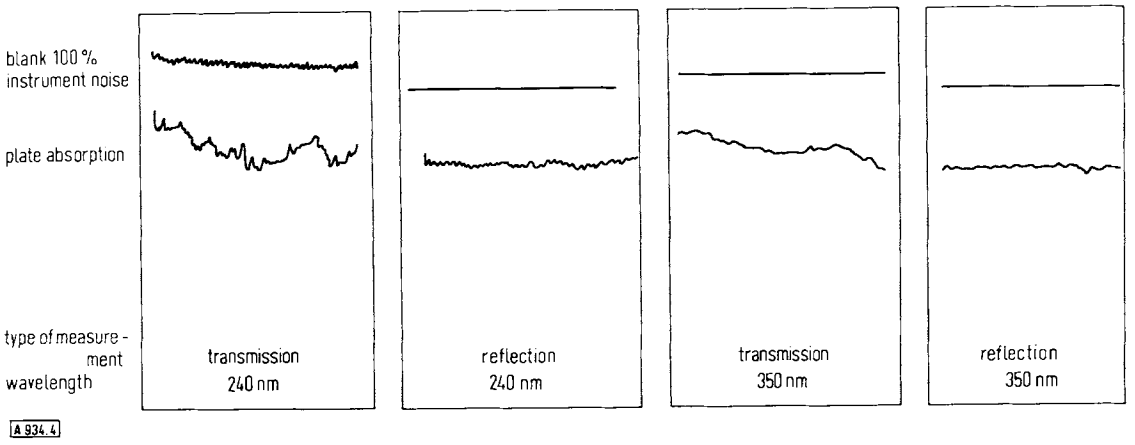

Fig. 4. Comparison of the plate background for reflection and transmission. Measurements on the same track, silica gel layer on quartz supporting plate.

the measuring beam and the reference beam in a double-beam arrangement, this difference appears additively in the result, and hence with an absolute value of $\Delta E = 0.009$.

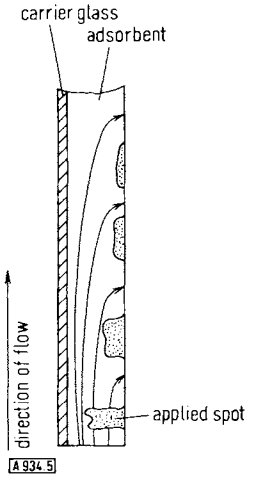

Fig. 5. Schematic representation of the spot penetration depth as a function of the R_f value of the spots [28].

This leads to considerable relative errors, particularly at low concentrations. For 0.2 µg of Sudan Red, one obtains a maximum extinction of about 0.1, and an error of 9% would therefore have to be expected in the above example.

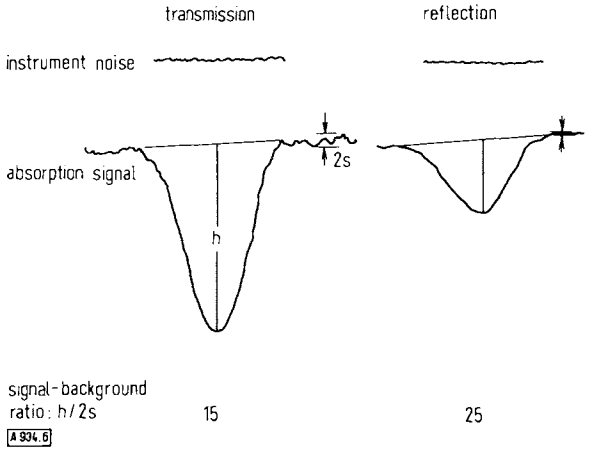

Fig. 6. Comparison of the signal-to-background ratios in reflection and in transmission for 1.25 µg of Butter Yellow at $\lambda = 440$ nm.

4. Determination of Absorption by Simultaneous Reflection and Transmission Measurements[29]

As can be seen from Figure 7, the detection limit in the direct photometric evaluation of TLC plates is determined not by the equipment noise but by the inhomogeneities in the adsorbent layer, which produce differences in scattering from place to place. It is found, however, that for reflection and for transmission measurements, these fluctuations from place to place will be exactly complementary;

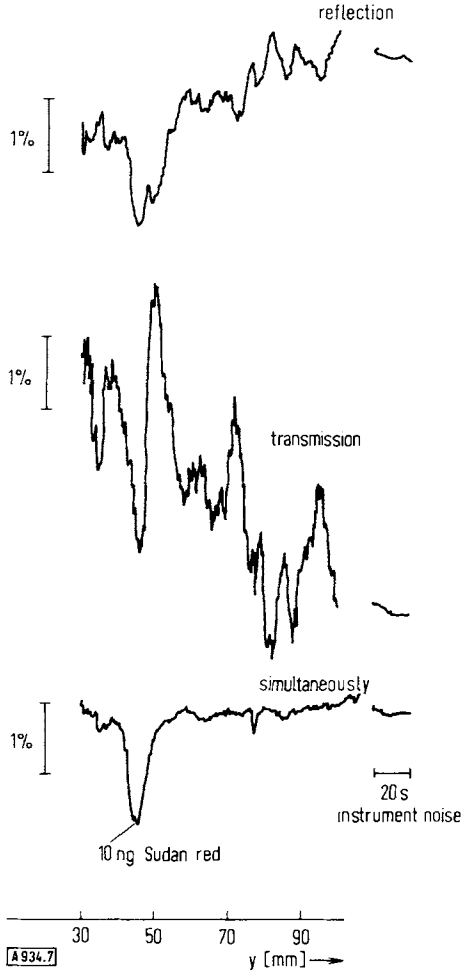

Fig. 7. Absorption measurement on 10 ng of Sudan Red on Merck commercial silica gel plate, solvent: benzene; measuring wavelength 500 nm, slit: 0.1 × 10 mm².

a decrease in transmission due to scattering on the unspotted and hence non-absorbing plate background means an increase in reflection. True absorption, on the other hand, *e.g.* due to a TLC spot, reduces the measured value both in reflection and in transmission. If the reflection signal and the transmission signal are added together, therefore, the baseline is smoothed out at a certain ratio of the magnitudes of these two signals, and at the same time the measured absorption value for the TLC spots becomes greater than in the pure reflection measurement (Fig. 7). This greatly improves the signal-to-background ratio; thus as little as 5 ng of Sudan Red can be detected directly by this method.

The quantitative evaluation of 10—100 ng of Sudan Red is shown in Figure 8. In this range of very small absorptions, the area between the absorption curve and the baseline varies linearly with the concentration.

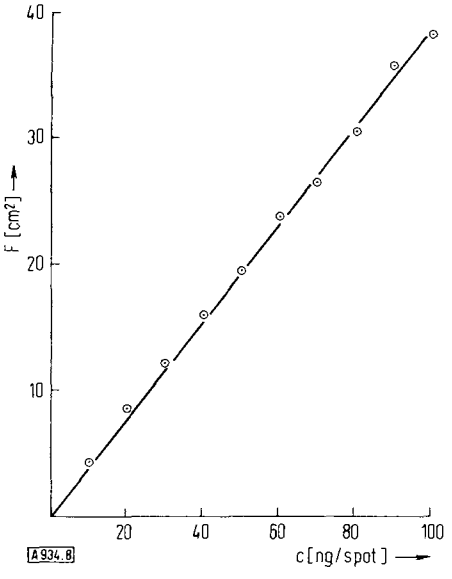

Fig. 8. Simultaneous measurement of reflection and transmission on 10—100 ng of Sudan Red; measuring wavelength 500 nm; amplification ratio reflection:transmission = 10:4, slit: 0.1 × 7 mm².

The method of simultaneous measurement is particularly effective in the visible region of the spectrum, since considerable penetration of the measuring radiation into the plate material occurs in this range.

An important feature of this method is that unlike in the double-beam method, the background is corrected at the actual point of measurement as a result of the retention of the single-beam principle.

5. Indirect Absorption Measurements by Diminution of Fluorescence in Reflection and Transmission

The diminution of fluorescence (often erroneously referred to as fluorescence quenching) is used in the visual investigation of TLC spots that absorb only in the UV region. This diminution of fluorescence is not a quenching phenomenon but an absorption effect[30, 31], generally for the 254 nm mercury line. The effect will be discussed below for the usual F_{254} plates (Fig. 9).

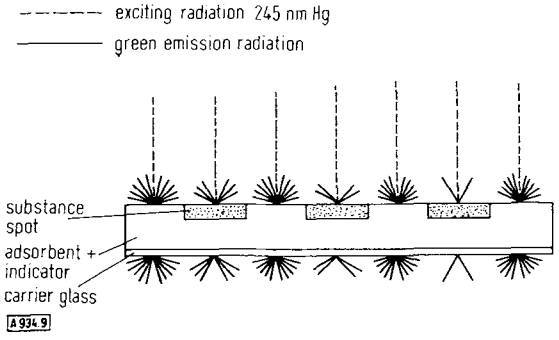

Fig. 9. Schematic representation of the diminution of fluorescence.

The adsorbent layer contains a fluorescence indicator, which fluoresces green on excitation (with 254 nm mercury line). If there is a spot on the TLC plate that absorbs the 254 nm radiation, it acts as a filter; this means that the quantity of exciting light falling on the indicator is reduced, with the result that less fluorescence light is produced at this point. The UV-absorbing spot therefore appears darker against the intensely green fluorescent background. The filter effect becomes stronger with increasing concentration of the substance, so that the spots appear correspondingly darker. This effect can also be used for the direct quantitative determination of UV-absorbing substances.

For non-scattering objects, the decrease of the green fluorescence, in transmission, would obey the Beer-Lambert law. The glass support of the TLC plate generally acts as a barrier filter for the exciting radiation in transmission measurements. The result of such a measurement is shown in Figure 10, curve 1, in which $\int E\,dy$ for the individual

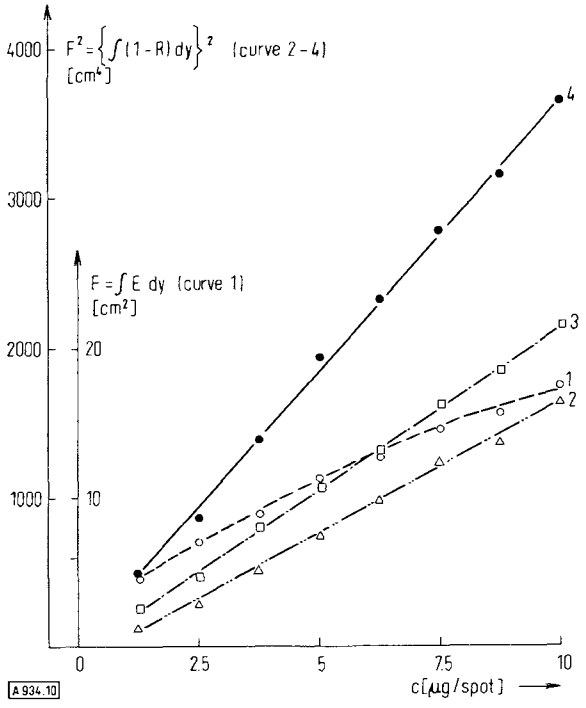

Fig. 10. Calibration series for caffeine, absorption measurement. Curve 1: diminution of fluorescence at 254 nm Hg in transmission, evaluation from the area in extinction units; curve 2: diminution of fluorescence at 254 nm Hg in reflection, evaluation from the square of the area; curve 3: reflection at 275 nm, evaluation from the square of the area; curve 4: combined reflection and diminution of fluorescence at 275 nm, evaluation from the square of the area.

spots is plotted *versus* the concentration. As in transmission measurements in the visible region of the spectrum (Fig. 1, curve 3), it can again be seen that the Beer-Lambert law is not obeyed because of scattering, and curved calibration lines are obtained. On the other hand, if the diffusely reflected fluorescent light is measured, a straight calibration line is again given by a plot of the square of the area (Fig. 10, curve 2). The scattered exciting radiation is cut off in this case by a secondary filter. As expected transmission measurements again offer no advantages over reflection measurements for evaluation based on the diminution in fluorescence. It still remains to check whether the measurement of the diminution in fluorescence is advantageous in comparison with absorption measurements in reflection.

The diminution in fluorescence measures only the absorption of the TLC spots at the wavelength at which the indicator is excited, *i.e.* generally at 254 nm. Normally, for substances whose absorption maximum does not happen to correspond to this wavelength, the measurement of diminution in fluorescence means a loss in sensitivity in relation to reflection measurement at the wavelength of maximum absorption. This effect is demonstrated in Figure 11, curves 1 to 4, for a mixture of drugs, whose

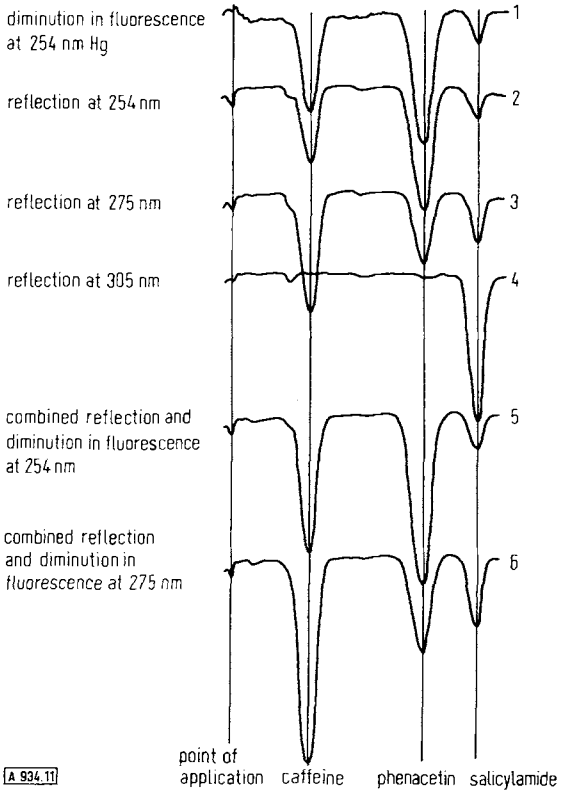

Fig. 11. Absorption-location curves for a mixture of drugs in reflection, diminution of fluorescence, and combined reflection and diminution of fluorescence.

principal components are caffeine ($\lambda_{max} = 275$ nm), phenacetin ($\lambda_{max} = 250$ nm), and salicylamide ($\lambda_{max} = 305$ nm) (spectra: Fig. 12). The reflection-location curves measured at various wavelengths are compared with the curve obtained by measurement of the diminution of fluorescence. The loss of sensitivity is particularly pronounced in the case

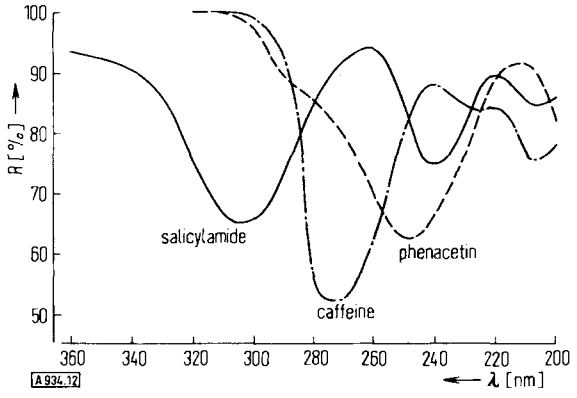

Fig. 12. Reflection spectra for 4 µg of caffeine, phenacetin, and salicylamide, based on silica gel.

of salicylamide. The value recorded on measurement of the diminution of fluorescence with excitation at 254 nm is only one sixth of the value recorded by a reflection measurement at the absorption maximum of 305 nm.

Determinations based on the diminution of fluorescence are therefore comparable with measurements using a filter photometer that allows measurements at only one wavelength, *e.g.* 365 nm, for all colored substances.

Though the measurement of the diminution of fluorescence offers no advantages as such, F_{254} plates are preferred in practice, since they allow a fast visual check on the chromatography. In addition to the less effective method based on the diminution of fluorescence (Fig. 10, curves 1 and 2), there are two methods for the quantitative evaluation of samples of this type.

The first method is monochromatic detection of the reflection with polychromatic radiation. In this case the measured value is practically unaffected by the fluorescence of the indicator. This pure absorption measurement in reflection satisfies the Kubelka-Munk law and is evaluated as the square of the area, as explained earlier (Fig. 10, curve 3; Fig. 11, curves 2—4).

The other method is to expose the plate to monochromatic radiation at the wavelength of the characteristic UV absorption of the substance in question. This light is reflected. Since the F_{254} plates not only exhibit fluorescence on excitation with 254 nm light, but can be excited over the entire UV range down to about 235 nm, this measuring arrangement also leads to the production of long-wave fluorescent radiation, which also falls on the photomultiplier. The reflected and the fluorescent light are both weakened by absorption in the spot in accordance with the Kubelka-Munk law. Since the absorption occurs at the same wavelength in both cases, the extinction coefficients ε are identical, but the scattering coefficients s for the short-wave reflected radiation and the long-wave fluorescent radiation are different. For this reason, combined measurement of the reflection and the diminution of fluorescence gives a stronger measured signal than pure absorption measurements in reflection. Theoretically the combined reflection and fluorescence measurements do not satisfy the Kubelka-Munk function. It is found in practice, however, that satisfactory straight calibration lines can also be obtained for this method by the approximation based on the square of the area (Fig. 10, curve 4).

6. Fluorescence Measurements

Fluorescent substances can also be investigated directly on the TLC plate. Just as in solution, the fluorescence intensity is directly proportional to the quantity of substance in the spot if the absorption is sufficiently low. A uniform distribution of the substance is no longer necessary, and the total fluorescence of the spot can be recorded all at once[32]. This can be achieved with a circular measuring area slightly larger than the TLC spots to be investigated.

In analogy with fluorescence photometry in solution, the fluorescence intensity obeys the law[13]:

$$I_{fl} \sim I_0(1-10^{-\varepsilon c d})$$

I_{fl} = fluorescence intensity
I_0 = intensity of incident light
ε = extinction coefficient
c = concentration
d = effective optical path in substance

For small extinctions $E=\varepsilon \cdot c \cdot d$ (roughly for $E<0.02$), the above equation can be approximated[13,32-35], within the accuracy of the measurements, by

$$I_{fl} \sim E \sim c$$

This linear relation between the fluorescence intensity and the concentration is used in quantitative fluorimetry. The validity of the laws can be demonstrated *e.g.* for Rhodamine B. The maximum excitation occurs at 546 nm Hg, and the emission maximum is found at 580 nm. Figure 13 shows calibration curves for 0.02—4 µg of Rhodamine

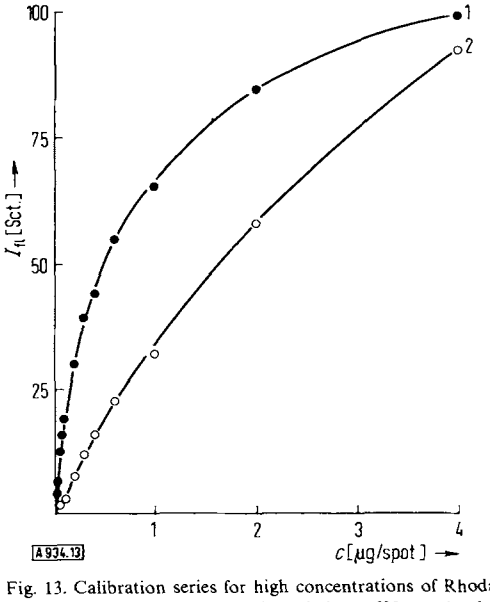

Fig. 13. Calibration series for high concentrations of Rhodamine B on excitation with 546 and 365 nm Hg, emission at 600 nm, circular measuring area.
Curve 1: excitation with 546 nm Hg; curve 2: excitation with 365 nm Hg.

B for excitation with various mercury lines. On excitation with 546 nm light, the linear range extends to approximately 0.1 µg per spot. For 365 nm light, the extinction coefficient, and hence also the extinction, of Rhodamine B is lower by a factor of about 10 than at 546 nm. The measuring sensitivity at 365 nm is accordingly lower by a factor of 6, but the extinction is so low even for 1 µg that the linear relation is valid up to this concentration.

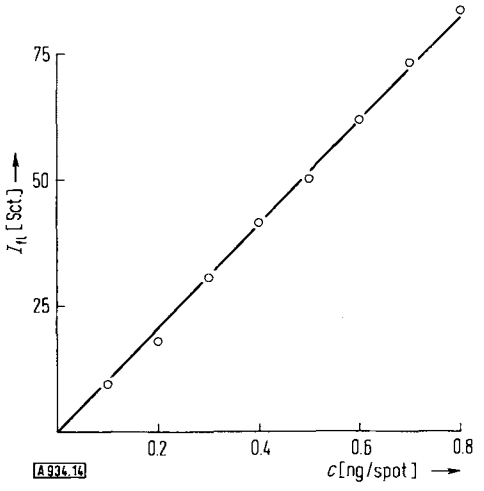

Fig. 14. Calibration series for low concentrations of Rhodamine B on excitation with 546 nm Hg, emission at 600 nm, circular measuring area.

In practice, the lower absorption is achieved with low concentrations. Thus on excitation with 546 nm light, for example, an excellent straight calibration line is obtained for 0.1—0.8 ng of Rhodamine B (Fig. 14). The detection limit is approximately 10^{-2} ng of Rhodamine B (Fig. 15).

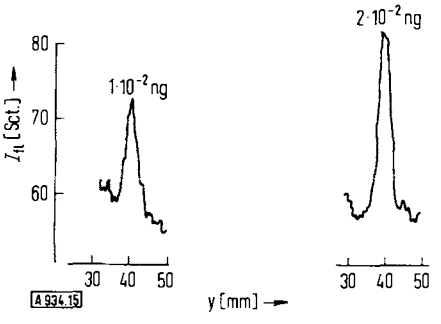

Fig. 15. Detection limit for Rhodamine B; fluorescence measurement on Merck commercial silica gel plate. Solvent: *n*-butanol/acetic acid/water (40:10:50); flow distance 7 cm; excitation at 546 nm Hg, emission at 590 nm, measuring area: $0.3 \times 6\,mm^2$.

The location resolution with a circular measuring area is limited by the diameter of the area. Measurement with a slit is therefore preferable for overlapping spots. Figure 16 shows the plot of fluorescence *versus* location as recorded with a measuring area in the form of a slit for aflatoxins B_1, B_2, G_1, and G_2. The quantitative evaluation must naturally be based on the area under the curve in this case. This gives a straight calibration line as shown in Figure 17 for aflatoxin B_1, with the aid of which it was possible to determine 1.22 ng of aflatoxin B_1/µl of sample solution with an accuracy of 4%[*].

[*] I am grateful to Mr. *Lorenzen*, Landwirtschaftliche Untersuchungs- und Forschungsanstalt, Bonn, for the aflatoxin samples.

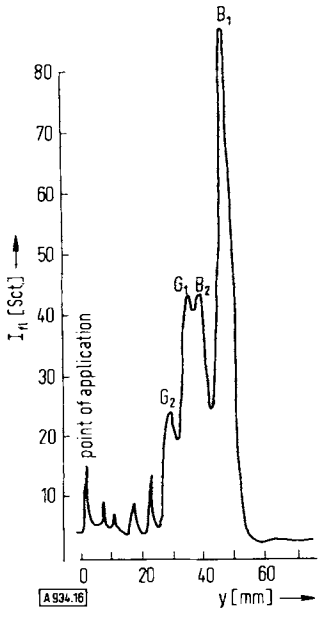

Fig. 16. Fluorescence location curve for aflatoxins B_1, B_2, G_1, and G_2; excitation with 365 nm Hg, emission at 435 nm, slit-shaped measuring area.

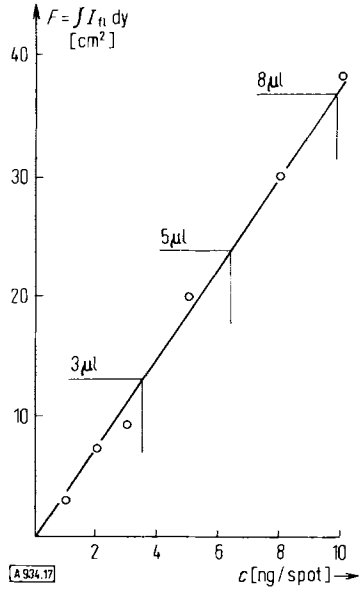

Fig. 17. Calibration series for aflatoxin B_1 and determination of the content in a sample solution; excitation with 365 nm Hg, emission at 435 nm, slit-shaped measuring area.

µl of sample solution	ng of aflatoxin B_1
3	3.5
5	6.4
8	9.8

Average (1.22 ± 0.05) ng/µl of sample solution.

7. Equipment

All the measurements were carried out with a Zeiss chromatogram spectrophotometer in combination with a Servogor recorder (Metrawatt) or a logarithmic integrating recorder W + W 3218 (Kontron).

The setup generally used for reflection measurements is a follows (Fig. 18a). Light from a tungsten or hydrogen lamp passes through a quartz monochromator and an achromatic imaging lens system to the sample. The light scattered here is measured at an angle of 45° with a photomultiplier. The measured value is amplified and passed to a pen recorder. The slit-shaped measuring area is produced by a 1:1 image of the entry slit of the monochromator on the sample. The slit is adjusted to the size of the spot by means of slip-in diaphragms (3.5—14 mm) fitted in the monochromator. The TLC plate is placed on a motorized stage; the chromatogram track can then be passed under the slit-shaped measuring area, and one thus obtains the reflection-location curve for the quantitative evaluation. Reflection measurements down to $\lambda = 190$ nm are possible with this arrangement.

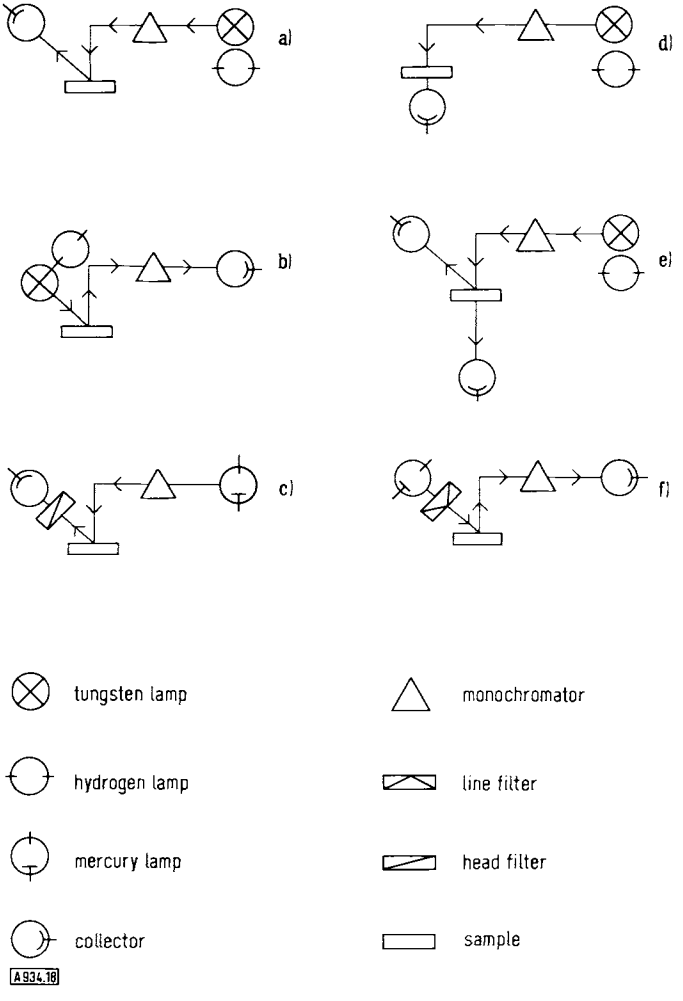

Fig. 18. The most important measuring arrangements for the Zeiss chromatogram spectrophotometer.
a) Absorption measurement in reflection and in combined reflection and fluorescence diminution; b) absorption measurement in reflection with interference by fluorescence; c) absorption measurement by diminution of in fluorescence, excitation preferably at 254 nm Hg; d) absorption measurement in transmission; e) simultaneous absorption measurement in reflection and in transmission; f) fluorescence measurement on excitation with Hg lines.

For reflection measurements where it is desirable to exclude fluorescence, *e.g.* fluorescence from the spot itself or the fluorescence of the plate background, the beam path is reversed (Fig. 18b). The sample is now irradiated with

polychromatic light, but only light of the desired reflection wavelength reaches the detector through the monochromator.

For measurement of the diminution of fluorescence (Fig. 18c), an medium-pressure mercury lamp type St 41 is fitted in the lamp-house to the right of the monochromator instead of the tungsten lamp. The Hg resonance line at 254 nm is selected with the monochromator. To cut out the exciting radiation, a secondary barrier filter ($\lambda_{barrier} \approx 460$ nm) is inserted between the sample and the detector.

For combined measurement of the reflection and the diminution of fluorescence on F_{254} plates, the same arrangement is used as for normal reflection measurements (Fig. 18a).

For transmission measurements, the sample is illuminated perpendicularly from above, and the detector is placed under the plate (Fig. 18d).

For the simultaneous measurement of reflection and transmission, the sample is again illuminated perpendicularly from above; the diffusely reflected light is measured at an angle of 45°, and the transmitted light at an angle of 0° under the sample (Fig. 18e).

For fluorescence measurements, the sample is illuminated with an Hg medium-pressure mercury lamp type St 41 at an angle of 45° (Fig. 18f). The mercury lines are selected by primary filters. An interchangeable lens in the measuring head, combined with an iris diaphragm, is used to obtain a circular measuring area, so that the total fluorescence of the TLC spot can be measured with direct integration. Only the emission radiation reaches the receiver through the monochromator. Where separation of the spots is poor, the slit-shaped measuring area is used because of its better location resolution.

8. Preparative

The caffeine/phenacetin/salicylamide mixture, Sudan Red, Butter Yellow, and Rhodamine B were chromatographed on Merck commercial silica gel plates. Merck Uvasols were used as solvents and developers. The aflatoxins were determined on Macherey and Nagel commercial silica gel plates.

The solutions were applied with a gas-tight 250 µl syringe (Hamilton) in combination with an Agla micrometer screw.

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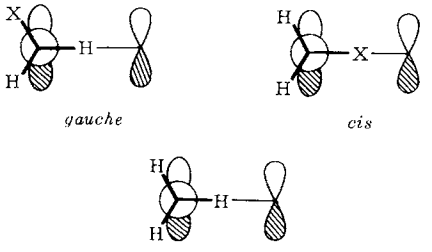
Semiquantitative Proof of Hyperconjugation[1]

By *Hartmut Schmidt* and *Armin Schweig*[*]

In recent years hyperconjugation[2] has again come much into the foreground of chemical research[3]. Using photoelectron (PE) spectra of allyl halides, we here describe the first semiquantitative proof of hyperconjugation.



Allyl halides CH_2=CH—CH_2X (X = F, Cl, Br or I) exist as *gauche* and *cis*-conformers[4]. However, because of the different populations of the two isomers, only the *gauche* form can be observed in the PE spectra[4d,e].

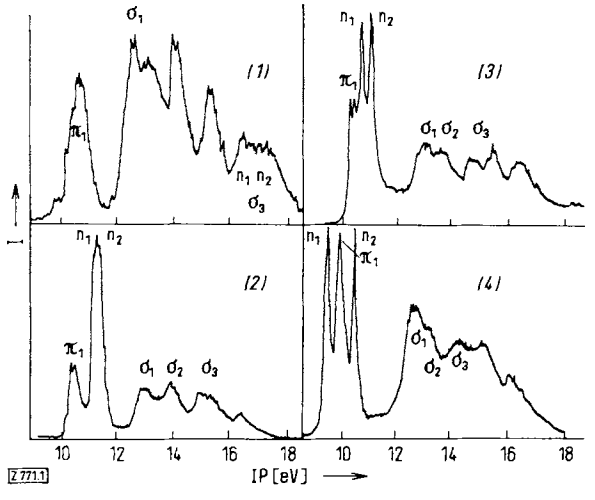


Fig. 1. Photoelectron spectra of allyl fluoride *(1)*, allyl chloride *(2)*, allyl bromide *(3)*, and allyl iodide *(4)*.

Figure 1 shows the PE spectra of the allyl halides, and Figure 2 shows the correlation diagram derived therefrom and from the PE spectrum of propene[3c]. π_1 is the highest occupied π-MO (antibonding combination of vinyl-π-MO and a π-combination of the CH_2X bonds). σ_1 couples the vinyl moiety to the substituents CH_2X. σ_2 and σ_3 are mainly localized in CH_2X, σ_3 being the C—X bonding MO. n_1 and n_2 are the MO's of the lone pairs of the halogen atoms; they are split by spin-orbit coupling[5].

We consider now the π_1-MO's. The electronic interactions between the vinyl-π-MO and the substituents CH_2X can be described, from models, by the hyperconjugative effect of the C—X and the C—H bonds (in the *cis*-conformation only the C—H bonds) and by the inductive effect of the halogen atoms.

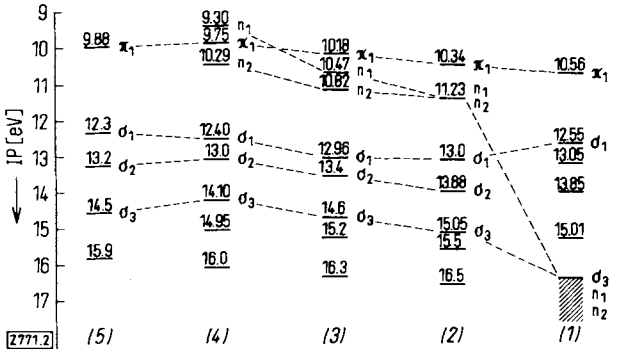


Fig. 2. Correlation diagram of the highest occupied MO's in propene *(5)* and the allyl halides *(1)* to *(4)*. The numbers above the levels denote vertical ionization potentials.

The hyperconjugative effect destabilizes π_1 (antibonding π-CH_2X combination), and the inductive effect stabilizes π_1 (F, Cl, Br and I are more electronegative than H). Our experimental results (Figs. 1 and 2) show that π_1 in allyl chloride *(2)*, bromide *(3)* and iodide *(4)* are destabilized (hyperconjugative interaction predominant) relative to the vinyl-π-MO (we selected as unperturbed vinyl-π-MO the $\pi(b_{1u})$-MO of ethylene, energy = −10.51 eV[6]); π_1 is stabilized only in allyl fluoride *(1)* (the particularly high inductive effect of the fluorine atom preponderates). The two interactions cannot be separated for allyl compounds. The inductive effect of the halogen atoms can, however, be estimated separately for the $\pi(a_2)$-MO[7] of the corresponding phenyl halides Ph—X (F = −0.58, Cl = −0.45, Br = −0.43, I = −0.18 eV[6]). If these inductive effects are subtracted from the observed total shifts of the π_1-MO's in the allyl compounds CH_2=CH—CH_2X (F = −0.05, Cl = 0.17, Br = 0.33 and I = 0.76 eV) there remain the bare hyperconjugative effects of the CH_2X substituents (F = 0.53, Cl = 0.62, Br = 0.76 and I = 0.94 eV).

In the allyl halides (*gauche* conformation) hyperconjugation is effective between the ethylene-π-MO on the one hand and one C—X and one C—H bond (both in *gauche* position) on the other. The hyperconjugative effect of the CH_3 substituent on π_1 in propene *(5)*, which exists only in one conformation[8], amounts to 0.63 eV[3c]. We can thus ascribe a value of 0.31 eV to the hyperconjugative effect of a C—H bond in the *gauche* position. If we subtract this C—H contribution from the hyperconjugative effects already determined for the CH_2X substituents, we finally obtain the hyperconjugative effects δE of the C—X bonds (F = 0.22, Cl = 0.31, Br = 0.45, and I = 0.63 eV)[9].

If hyperconjugation is a conjugation that can be described by the same bonding models as, for example, π-conjugation, then, applying the rules of simple perturbation theory, we must expect that δE will be indirectly proportional to the energy difference ΔE between the interacting MO's (basis MO's). As basis MO's we select, alongside the $\pi(b_{1u})$-MO of ethylene, the $\sigma(a_1)$-MO's (C—X MO's) of the methyl halides CH_3X (energies: F = −16.2[10], Cl = −14.4, Br = −13.5, I = −12.5 eV[6]).

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Plotting δE against $1/\Delta E$ gives a straight line which, as it must, passes exactly through the origin (Fig. 3). On the assumption that the interaction integrals between the various C—X bonding MO's and the $\pi(b_{1u})$-MO of ethy-

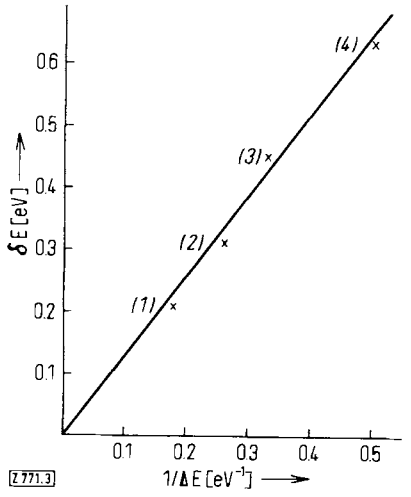

Fig. 3. A plot of δE against $1/\Delta E$.

lene do not differ much[11], this result provides a consistent confirmation of hyperconjugation as a conjugation mechanism that can be described by the same model as π-conjugation, and further provides an independent proof of the existence of hyperconjugation. From Fig. 3 we can also extract the series of hyperconjugative ability: C—F < C—Cl ≈ C—H < C—Br < C—I.

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Photoionization Cross Sections: Differing Relative Band Intensities in He-I and He-II Photoelectron Spectra[1]

By *Peter Dechant, Armin Schweig,* and *Walter Thiel*[*]

In the transition from He-I to He-II photoelectron spectra (photon energies 21.22 and 40.81 eV, respectively) intensity shifts often occur[2] (cf. Fig. 1) which are theoretically described by the energy-dependence of the corresponding photoionization cross sections. Within the framework of certain approximations (dipole approximation, *Koopmans'* theorem, description of the ionized molecular orbital (MO) by a valence-electron-LCAO—SCF—MO and of the orbital of the free photoelectron by a plane wave) the photoionization cross section σ_n of the n-th ionization process[3,4] is given by:

$$\sigma_n = A\, p_n \left[\sum_a Q_a^n + \sum_{a<b} Q_{ab}^n\right]/E_{ph} \qquad (1)$$

where A is a constant, p_n the momentum of the free photoelectron, and E_{ph} the irradiating photon energy. The one-center terms Q_a^n and the two-center terms Q_{ab}^n are composed of the contributions of the individual basis atomic orbitals (AO) $\phi_{a\nu}$ and their combinations $\phi_{a\nu}/\phi_{b\lambda}$ (atoms a, b; AO numbers ν, λ). They are dependent on the LCAO coefficients $c_{a\nu}$ of the ionized MOs, on the AO transition moments $M_{a\nu}$ (measure of the transition probability between the $\phi_{a\nu}$ AO and the orbital of the free photoelectron; conjugate complex $M_{a\nu}^*$) and on the interference terms $I_{\nu\lambda}$[4]:

$$Q_a^n = \sum_\nu c_{a\nu}^2\, M_{a\nu}\, M_{a\nu}^* \qquad (2)$$

$$Q_{ab}^n = 2\sum_\nu \sum_\lambda c_{a\nu}\, c_{b\lambda}\, M_{a\nu}\, M_{b\lambda}^*\, I_{\nu\lambda} \qquad (3)$$

In order to find the energy-dependence of the photoionization cross section it is generally necessary to investigate each quantity p_n/E_{ph}, Q_a^n and Q_{ab}^n of eq. (1) separately. In ionization processes with similar ionization potentials IP_n the quotients p_n/E_{ph} are of approximately the same size. This is true particularly for high photon energies ($E_{ph} \gg IP_n$), so that in this case there is only a slight effect on the relative values of the photoionization cross sections. The two-center terms Q_{ab}^n are usually considerably smaller than the one-center terms Q_a^n (*inter alia*, for ionizations of lone pairs and for π-ionizations at high photon energies). Thus intensity shifts in photoelectron spectra can often be explained to a first approximation by variation in the one-center terms Q_a^n alone, as will be shown by the following examples:

Table 1 contains the calculated[5] and the experimental[6] values for the relative intensities of the highest bands in the He-I and He-II spectra of cyclopentadiene, pyrrole, furan, and phosphane. Figure 1 illustrates a section of the He-I and the He-II spectra of furan.

For the heterocycles among the five-membered rings investigated[7] it is found that, in agreement between theory and experimental investigations, the second band (π-MO with non-zero coefficient at the hetero atom, symmetry

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Table 1. Vertical ionization potentials [7, 8] and relative band intensities of cyclopentadiene, pyrrole, furan, and phosphane. The standard deviations given each refer to five determinations of the spectrum.

Molecule	MO	*IP* [eV]	Helium (I)			Helium (II)		
			CNDO	MINDO	Exp.	CNDO	MINDO	Exp.
C_5H_6	a_2	8.57	88	89	98±3	96	97	98±2
	b_1	10.72	100	100	100	100	100	100
C_4H_4NH	a_2	8.21	100	100	100	100	100	71±4
	b_1	9.20	72	76	89±4	100	98	100
C_4H_4O	a_2	8.88	100	100	100	100	100	76±5
	b_1	10.31	60	80	84±2	88	89	100
PH_3	a_1	10.60	43	—	47±2	23	-	39±1
	e	13.6	100	—	100	100	—	100
	a_1	19.0	—	—	—	10	—	<15

b_1) in the He-I spectra is less intense than the first band (π-MO with node at the hetero atom, symmetry a_2) but that its intensity increases significantly on going to the He-II spectrum. Because of the symmetry of the MOs the 2p-AO of the hetero atom provides a one-center contribution [eq. (2)] to the photoionization cross section only for the b_1- and not for the a_2-MO. As shown in Figure 2, this contribution increases relatively sharply on transition from the He-I to the He-II spectrum, since M_{av} M^*_{av} of the 2p-AO transition moments for nitrogen and oxygen in the He-I energy region is considerably less than for carbon but in the He-II energy region is approximately the same. The differing intensities of the two uppermost π-bands in the He-I and the He-II spectra of pyrrole and furan are thus to be ascribed to the differences in the one-center contributions from the hetero atom. As is to be expected theoretically, there is no corresponding intensity shift with the homologous cyclopentadiene.

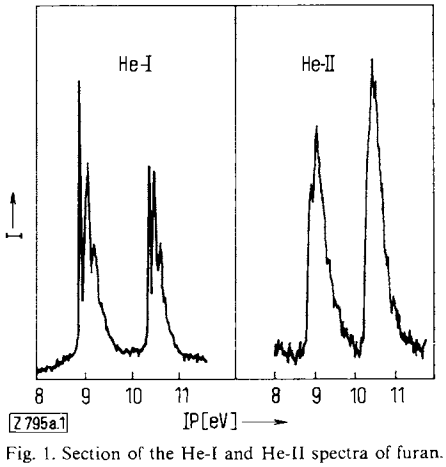

Fig. 1. Section of the He-I and He-II spectra of furan.

For phosphane[2b, 8], a decrease in intensity of the highest band (a_1, lone pair on the phosphorus) and a very low intensity of the lowest band (a_1, PH-bonding) is observed on transition to the He-II spectrum. The two a_1-MOs each have high 3s coefficients whereas for symmetry reasons the e-MO (PH-bonding) has no 3s component. According to Figure 2 the low intensity of the a_1 bands in the He-II spectrum can be ascribed to the great decrease in the transition moments of the phosphorus 3s AO at higher kinetic energies of the photoelectron.

The two cases discussed demonstrate how, to a first approximation, band intensities in photoelectron spectroscopy can be interpreted by means of the LCAO coefficients (electron density distribution) in the ionized MO and of

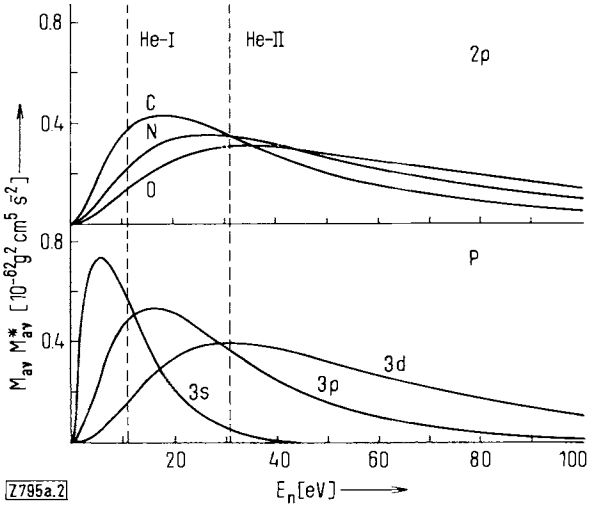

Fig. 2. Squared amounts $M_{av}M^*_{av}$ of the transition moments of some basis AOs as a function of the kinetic energy E_n of the free photoelectron ($E_n = E_{ph} - IP_n$). The two broken lines show the photoelectron energies that appear on He-I and He-II excitation at an ionization potential of 10 eV.

the energy-dependent transition moments of the basis AOs. Since, qualitatively, the intensity shifts (He-I/He-II) are correctly predicted, the procedure appears useful as an aid in assignments.

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[5] The input data required are the experimental geometries, vertical ionization potentials, and CNDO/2 or MINDO/2 eigenvectors.

[6] The measurements were carried out with a Perkin-Elmer PS-16 spectrometer fitted with a He-II lamp and an electronic integrator. To correct for dispersion the experimental values were all divided by the mean kinetic energy of the emitted photoelectrons. The influence of the asymmetry parameter β of the angular distribution on the experimental differential photoionization cross sections was neglected.

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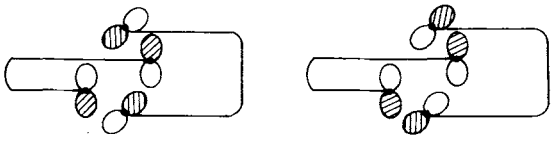
Spiroconjugation[1]

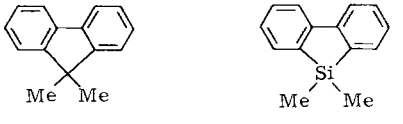
By *Armin Schweig, Ulrich Weidner, Dieter Hellwinkel,* and *Wolfgang Krapp*[*]

When two π-systems are perpendicular to one another and linked by one tetrahedral atom, interaction by spiroconjugation[2] can occur between those MOs of the two systems whose terminal $2p_\pi$-AOs ($2p_\pi$-AOs on the atoms next to the tetrahedral atom) are each antisymmetric to one another[3]. These antisymmetric $2p_\pi$-AOs in each of the two partial systems can adopt either of two arrangements with respect to each other: (A) spiroantibonding and (B) spirobonding. The difference between the energies of the spiroantibonding (A) and the spirobonding (B) combinations is called "spiro splitting".



(A) *(B)*

The concept of spiroconjugation was originally developed for spiro compounds. In previous papers[4] we provided, by photoelectron spectroscopy, the first evidence for spiroconjugation in the structurally similar but non-spiro compounds tetravinylmethane $(CH_2{=}CH)_4C$ *(5)* and tetravinylsilane $(CH_2{=}CH)_4Si$ *(6)*. For these compounds we had to rely on assumptions concerning molecular geometry (D_{2d} symmetry), since this is not fixed by ring formation as it is for spiro compounds. In addition, problems arise with assignment, since in the π-systems of dimethyldivinylmethane $(CH_3)_2C(CH{=}CH_2)_2$ and dimethyldivinylsilane $(CH_3)_2Si(CH{=}CH_2)_2$ the energy separation of the HOMO ("highest occupied MO") not capable of spiroconjugation and the MO immediately below this which takes part in spiroconjugation is smaller than the splittings that occur (Jahn-Teller splitting of the HOMOs and spiro splitting of the lower MOs). These problems can be avoided by studying spiro compounds of suitable structure (the HOMOs of the two rings are capable of spiroconjugation and lie sufficiently far above the other π-MOs). We have thus been able to provide direct, unambiguous evidence for spiroconjugation by means of the photoelectron (PE) spectra of 9,9-dimethylfluorene *(1)*, 9,9-dimethyl-9-silafluorene *(2)*, 9,9′-spirobifluorene *(3)*, and 9,9′-spirobi(9-silafluorene) *(4)*.



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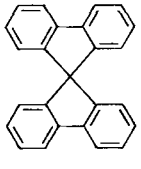

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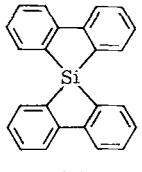

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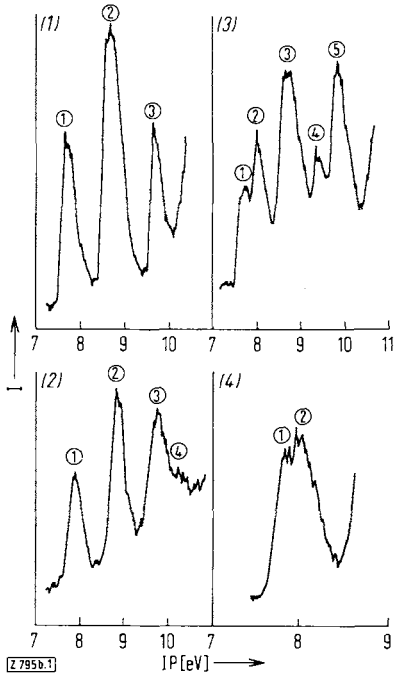
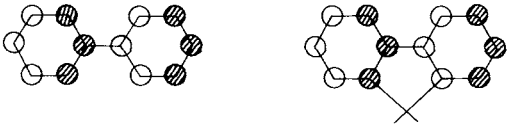


Fig. 1. Photoelectron spectra [9] of 9,9-dimethylfluorene *(1)*, 9,9-dimethyl-9-silafluorene *(2)*, 9,9′-spirobifluorene *(3)*, and 9,9′-spirobi(9-silafluorene) *(4)*. The vertical ionization potentials (in eV) and relative intensities are: For *(1)*: ① 7.8/1, ② 8.75/1.8, ③ 9.75/1.0; for *(2)*: ① 7.9/1, ② 8.80/1.5, ③ 9.7, and ④ 10.25/2.7; for *(3)*: ① 7.7/1, ② 8.0/1.3, ③ 8.7/3.2, ④ 9.4/1.3, and ⑤ 9.9/3.0; for *(4)*: ① 7.85 and ② 8.0/2, ③ 8.85 and ④ 9.1/3.7, ⑤ 9.85/2, and ⑥ 10.25/3 [10].

Figure 1 shows the PE spectra of *(1)* to *(4)*. The spectra of *(1)* and *(2)* show the same signal structure (intensities of ①:②:③ = 1:2:1) as for biphenyl *(7)*[5]. It follows that the highest occupied MOs of *(1)* and *(2)* are closely related to the corresponding MOs in *(7)* and thus in particular that the HOMO in *(1)* and *(2)* is capable of spiroconjugation (the $2p_\pi$-AOs of the atoms 8a and 9a next to the tetrahedral atom are antisymmetric) [cf. the representation of the HOMOs of *(7)* and *(1)* or *(2)*].



As thus anticipated, we observe splitting of signal ① in the PE spectra of *(1)* and *(2)* into two signals ① and ② in the PE spectra of *(3)* and *(4)*. It amounts to 300 meV for *(3)* and 180 meV for *(4)*. Since the splitting is in each case smaller than the separation of signal ① from signal ② in the spectra of *(1)* and *(2)* no problem of interpretation or assignment arises.

The ratio of the spiro splittings for compounds *(4)* and *(3)* amounts to 180/300 = 0.60 and is thus almost the same as the corresponding ratio for compounds *(6)* and *(5)* 450/730 = 0.62[4]. So the spiro splitting decreases by about 60% on replacement of the tetrahedral C atom (the spiro atom in the spiro compounds) by an Si atom.

If the tetrahedral atom remains the same, the spiro splitting of two different MOs capable of spiroconjugation should

behave as the square of the $2p_\pi$-AO coefficients of the atoms next to the tetrahedral atom. The observed ratio of the spiro splittings for compounds *(3)* and *(5)* (*i.e.* in the carbon series) is 300/730 = 0.41. The analogous ratio in the silicon series, 180/450 = 0.40, is in good agreement with that. The ratio estimated from MINDO/2 coefficients[6] is $(0.34)^2/(0.47)^2 = 0.52$.

(8)

After these results we expect for the newly synthesized spiro[4.4]nonatetraene *(8)*[7] an HOMO splitting of $[(0.56)^2/(0.34)^2]\cdot 0.3\,\text{eV} = 0.8\,\text{eV}$ or $[(0.56)^2/(0.47)^2]\cdot 0.7\,\text{eV} = 1.0\,\text{eV}$, *i.e.* about $0.9 \pm 0.1\,\text{eV}$[8].

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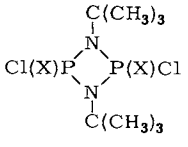
[10] Investigations of the assignment of the higher PE bands, not discussed here, will be reported elsewhere.

Crystal Structure of 1,3-Di-*tert*-butyl-2-*trans*-4-dichloro-2,4-dioxo-1,3,2λ⁵,4λ⁵-diazadiphosphetidine; Stereochemistry of Oxidation at Phosphorus(III) by Dimethyl Sulfoxide

By *Rodney Keat*, *Ljubica Manojlović-Muir*, and *Kenneth W. Muir*[*]

The oxidation of phosphorus(III) compounds by dimethyl sulfoxide constitutes a useful route to oxophosphoranes[1], although nothing is known of its stereochemical features. To shed more light on this aspect of the oxidation process and on the structure of a dioxocyclodiphosphazane, for which no detailed structural information is available[2], we have examined the crystal structure of 1,3-di-*tert*-butyl-2,4-dichloro-2,4-dioxo-1,3,2λ⁵,4λ⁵-diazadiphosphetidine *(2)*.



(1), X = lone pair
(2), X = O

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Compound *(2)* was obtained as a crystalline, air-stable solid (m.p. 139—140 °C) by oxidation of the analogous phosphorus(III) compound *(1)* by dimethyl sulfoxide in methylene chloride solution at −78 °C. A ^{31}P-NMR spectrum of the reaction products showed only one signal at +7.5 ppm (from external H_3PO_4), indicating that only one isomer was formed. No evidence has obtained for the presence of a second isomer.

Compound *(2)* crystallizes in the tetragonal space group $P4_2/n$; a cell of dimensions $a = 13.428$, $c = 8.152$ Å contains four molecules, each of which is required to possess C_i symmetry. The intensities of all reflections with $\theta(Mo_{K\alpha}) \leq 30°$ were measured on a PDP 8-controlled Hilger and Watts Y 290 diffractometer. Least squares refinement (841 observations significantly above background, 110 parameters) converged with $R = 0.036$ and $R_w = 0.042$. The results are summarized in Table 1 and Figure 1. Since there are no significant differences between chemically equivalent bond lengths or interbond angles, appropriate average values are presented in the Table.

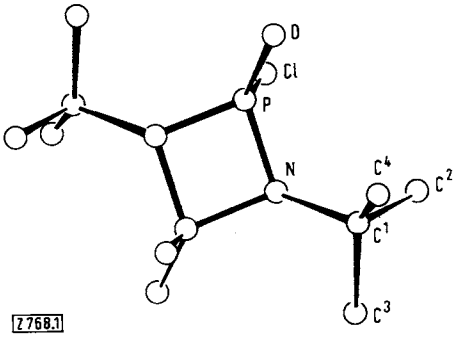


Fig. 1. Perspective view of one molecule of *(2)* (hydrogen atoms omitted for clarity).

Table 1. Mean bond lengths [Å] and interbond angles [°] in the diazadiphosphetidine *(2)*.

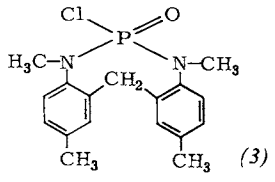
P—Cl	2.007(2)	Cl—P—O	109.5(1)
P—O	1.448(3)	Cl—P—N	108.2(2)
P—N	1.661(5)	O—P—N	121.5(8)
N—C	1.507(5)	N—P—N′ [a]	85.5(2)
C—C	1.518(7)	P—N—P′ [a]	94.5(2)
C—H	1.00(2)	P—N—C	131.9(18)

[a] Primed atoms are related to corresponding unprimed atoms by an inversion center.

The most striking feature of the structure of *(2)* is that the chlorine atoms are arranged *trans* to each other, whereas they are mutually *cis* in the precursor *(1)*. Thus the oxidation of *(1)* to *(2)* is, within experimental error, stereospecific and involves both inversion and retention of configuration at phosphorus. We are at present unable to decide whether this unusual result has kinetic or thermodynamic origins. In contrast, retention of configuration at phosphorus was observed on oxidation of cyclic phosphites by HNO_3 and by N_2O_4[3].

The P—Cl and P—N distances in *(2)* are respectively 0.098(9) and 0.028(7) Å shorter than the corresponding distances of 2.105(9) and 1.689(5) Å in *(1)*[4]. It has recently been shown that a similar slight shortening of P^{III}—N bonds occurs on formation of a P^V-sulfide[5]. Comparison with the bond lengths about the approximately tetrahedral phosphorus atom in the heterocycle *(3)*[6] is interesting in that the exocyclic P=O and P—Cl bonds (respectively 1.492(5) and 2.069(3) Å) are appreciably longer than the corresponding bonds in *(2)*, while the P—N distance in

(3) of 1.644(6) Å is comparable with that in *(2)*. This implies a strengthening of the P=O and P—Cl bonds when the N—P—N angle is decreased; in fact these bonds in *(2)* are comparable in length with those in $POCl_3$ (1.456(10) and 1.976(7) Å respectively)[7] and in $Cl_2P(O)$—$NC_6H_5P(S)Cl_2$ (1.449(6) and 1.969(6) Å respectively)[5], where the phosphorus atoms are highly electrophilic. However, in view of these differences, it is surprising that the P—N bond length in *(3)* is not reduced more significantly relative to that in *(2)*.



(3)

The ring system in *(2)* is planar, whereas in *(1)* it was slightly puckered. This may be as much a function of the mutual orientation of the chlorine atoms as of the oxidation state of phosphorus, since the *trans* isomer of the structurally related dithiocyclodiphosphazane $[C_6H_5(S)P—NC_2H_5]_2$ has a planar ring, but in the *cis* isomer the ring is puckered[8].

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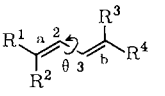
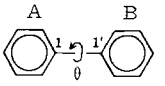
Ionization Potentials of Deformed π-Bonds[1]

By *Christopher Batich, Otto Ermer, Edgar Heilbronner*, and *John R. Wiseman*[*]

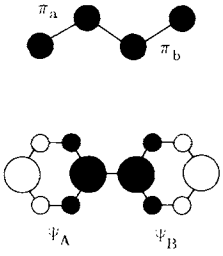
If two conjugated π-systems, each individually planar [*e.g.* the double bonds a, b in the diene *(1)* or the benzene rings A, B in biphenyl *(2)*] are twisted with respect to each other by an angle θ, then there is a noticeable effect on the position of the π-bands in the photoelectron (PE) spectrum of the compound in question[1-4]. If, in the sense of *Koopmans'* theorem[5], the vertical ionization potentials I_v are interpreted as negative orbital energies,



(1)



(2)



i.e. $I_{v,J} = -\varepsilon_J$, then it can be shown that the splitting Δ of the orbitals

$$\pi_+ = (\pi_a + \pi_b)/\sqrt{2}$$
$$\pi_- = (\pi_a - \pi_b)/\sqrt{2}$$

in *(1)* or the orbitals (1)

$$\psi_+ = (\psi_A + \psi_B)/\sqrt{2}$$
$$\psi_- = (\psi_A - \psi_B)/\sqrt{2}$$

in *(2)* can be described within the framework of a first order perturbation calculation referred to a simple LCMO model, by the relationships

$$(1):\ \Delta = \varepsilon(\pi_-) - \varepsilon(\pi_+) = -\beta_{23}\cos\theta$$
$$(2):\ \Delta = \varepsilon(\psi_-) - \varepsilon(\psi_+) = -\tfrac{2}{3}\beta_{11'}\cos\theta \quad (2)$$

The resonance integrals $\beta_{23} = \langle\phi_2|\mathscr{H}|\phi_3\rangle$ and $\beta_{11'} = \langle\phi_1|\mathscr{H}|\phi_{1'}\rangle$ are defined as usual for the 2p atomic orbitals of the coplanar system *(1)* or *(2)*, *i.e.* for θ = 0°. Calibration by means of the PE spectra of substituted compounds of types *(1)* and *(2)* whose angles of twist θ are known or can be estimated (substituted butadienes[2], cycloalkadienes[3], substituted biphenyls[4]) affords $\beta_{23} \approx \beta_{11'} \approx -2.5$ to -2.8 eV.

These successful applications of photoelectron spectroscopy to determination of the dependence on the angle of twist θ of the coupling between conjugated π-systems might lead one to suppose that this method would prove an ideal probe for characterizing twisted or otherwise deformed double bonds. We shall show that this is not the case or only so within very narrow limits.

Within a HMO model the resonance integral $\beta_{12} = \langle\phi_1|\mathscr{H}|\phi_2\rangle$ between the two 2p atomic orbitals ϕ_1, ϕ_2 of a two-center π-bond has a β_{12} value of at least ≈ -3.6 eV, as calculated from the above values with $\beta_{12} = \beta_{23}S_{12}/S_{23}$, where S_{12} and S_{23} are the overlap integrals for $R_{12} = 1.33$ and $R_{23} = 1.48$ Å. If one twists ϕ_1 and ϕ_2 by an angle θ, while keeping the distance R_{12} constant, the orbital energy $\varepsilon(\pi) = \alpha + \beta_{12}$ of the planar system (θ = 0°) is shifted by

$$\Delta\varepsilon(\pi) \approx 3.6(1 - \cos\theta)\,\text{eV} \quad (3)$$

For θ = 10, 20, 30 and 40° expression (3) gives the values $\Delta\varepsilon(\pi) \approx 0.05$, 0.22, 0.48 and 0.84 eV.

However, when applying formula (3) it must be remembered that non-planar deformations of the double bond of a system $R^1R^2C{=}CR^3R^4$ can be effected not only by a pure twist but also by out-of-plane (oop) bending, *i.e.* deformations with loss of coplanarity of the three σ-bonds that originate from each of the two C atoms. Thus, to characterize the deformation it is necessary to define both the twist angle (defined as the arithmetical mean of the

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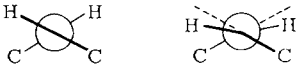
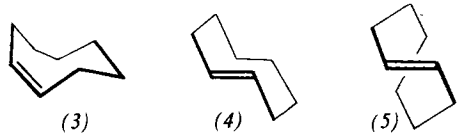
two *cis* torsion angles of a double bond) and two "oop-bending" parameters χ_1 and χ_2[6,7]. *Mock*[8], and also *Radom*, *Pople*, and *Mock*[9] have shown by theoretical calculations that both types of deformation must occur in conjunction if, for instance, a *trans*-C—CH=CH—C unit is twisted around the double bond, because the C—H bonds are then oriented as shown in (B) and not as one would have expected *i.e.* as in (A).



(A) (B)

It follows that the influence of χ_1 and χ_2 on $\Delta\varepsilon(\pi)$ must be complex, since apart from additional changes in β_{12} the amount of σ,π-interaction and the s-character of the basis orbitals ϕ_1, ϕ_2 also will change.



(3) (4) (5)

cis-cyclooctene
$I_a(\pi)$ = 8.82 eV
$I_v(\pi)$ = 8.98 eV

trans-cyclooctene
$I_a(\pi)$ = 8.53 eV
$I_v(\pi)$ = 8.69 eV

The most favorable conformation of *cis*-cyclooctene is very probably *(3)*[6,10,11] which can be derived from the chair-tub conformation of cyclooctane. In this case the π-bond is only minimally twisted if at all. The preferred conformation of *trans*-cyclooctene is not known with complete certainty. An electron diffraction study carried out recently by *Gavin* and *Wang*[12] was interpreted by the authors as showing that in the gas phase *trans*-cyclooctene has the chair conformation *(4)* with a C—C=C—C torsion angle of 23°, but other results favor the conformation *(5)* of C_2 symmetry that is related to the eight-membered ring crown conformation. X-ray analyses of two *trans*-cyclooctene derivatives afforded C—C=C—C torsion angles of 138°[13] and 134°[14]; energy minimization calculations yield the corresponding values of 138°[6] and 149°[11]. (Inserting these C—C=C—C torsion angles, which are certainly much too large for the free molecules, into eqn. (3) yields $\Delta\varepsilon(\pi)\approx 0.5$ to 1.1 eV, *i.e.* values that are unrealistically high.)

For the free molecules, energy-minimization calculations afford twist angles (as defined above) of 19.8°[6] and 16.3°[11], respectively, in which, however, *(5)* is predicted to be the more stable conformer. Independently of which conformation is the preferred one, if one uses $\theta\approx 16$ to 23° in eqn. (3), one obtains $\Delta\varepsilon(\pi)=0.14$ to 0.29 eV. However one should note that formula (3) is only a very crude approximation and leaves the influence of "oop-bending" deformations out of account. The observed difference in vertical (adiabatic) ionization potential $I_v(\pi)(I_a(\pi))$ between *cis*- and *trans*-cyclooctene amounts to 0.29 eV, which by eqn. (3) corresponds to an angle θ in our model of ≈23°, in agreement with expectation.

To obtain further insight into the dependence of the π-ionization potential on deformation of the π-bond, we have determined the PE spectrum of cyclooctyne *(6)*. In this compound the C_{sp}—C_{sp} bonds depart by *ca.* 21.5° from colinearity with the axis of the triple bond[15]. This should

(6)

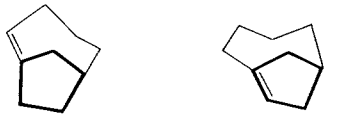
cyclooctyne
$I_a(\pi)\approx 8.9$ eV
$I_v(\pi)$ = 9.2 eV

noticeably lift the degeneracy of the two π-orbitals, but to a first approximation this is not the case. The spectrum of *(6)* shows a simple intense π-band, with little fine structure, at $I_v(\pi)=9.20$ eV with a halfwidth (HW) of 0.6 eV and no recognizable marked splitting [for comparison: diethylacetylene: $I_v(\pi)=9.25$ eV (HW = 0.5 eV); di-*n*-butylacetylene: $I_v(\pi)=9.06$ eV (HW = 0.5 eV)[16]]. From this result it must be concluded that the splitting of the two π-orbitals induced in *(6)* has a value of at most one vibrational quantum of the ionized C≡C bond, *i.e. ca.* 0.2 eV.

On the basis of these results it is not surprising that the PE-spectroscopic study of "anti-Bredt" hydrocarbons such as the pair of isomers bicyclo[4.2.1]non-1(2)ene *(7)* and bicyclo[4.2.1]non-1(8)ene *(8)*[17] provides little information. From energy calculations with an optimized valence force field (including important cross terms)[6] the conformations here schematically represented as *(9)* and *(10)* appear to be the most advantageous. The calculations give twist angles of 18.4 and 16.6°, respectively.

(7) *(8)*

$I_v(\pi)$ = 8.45 eV $I_v(\pi)$ = 8.37 eV



(9) *(10)*

From formula (3) and in view of our experience with the compounds *(3)*, *(4)* and *(5)*, the shifts here can hardly be expected to be greater than $\Delta\varepsilon(\pi)\approx 0.1$ to 0.2 eV. In fact the measured ionization potentials $I_v(\pi)=8.45$ and 8.37 eV for *(7)* and *(8)*, respectively, coincide within experimental error with the values that would be expected, on the basis of known data for unsaturated hydrocarbons, for a correspondingly substituted and fully planar π-bond.

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Direct Chemical Evidence for Energy Transfer between Identical Molecules[**]

By *Peter Lechtken* and *Nicholas J. Turro*[*]

Energy transfer in the solid state, especially in crystals, is a well-known and well-studied phenomenon[1]. However, with the sole exception of some studies employing the indirect technique of fluorescence depolarization[2], there exists little information in the literature concerning energy transfer between identical molecules in *fluid solution at room temperature*[3]. The difficulty in studying energy transfer between identical molecules in fluid solution resides in the absolute identity of the reactants and the products [Reaction (1)].

$$A^* + A \rightleftharpoons A + A^* \quad (1)$$

$$A^* + A \rightleftharpoons (AA)^* \rightleftharpoons A + A^* \quad (2)$$

Evidence for the occurrence of such an "energy hopping" between identical molecules is of great interest for:

a) unraveling the question of whether excimers[4] of ketones exist [(AA)*; Reaction (2)];

b) providing a novel mechanism for "long range" energy transfer;

c) understanding the factors which determine the duration of electronic excitation in a molecule.

The ability of tetramethyl-1,2-dioxetane *(1)* to produce high yields of excited singlet and triplet acetone upon photolysis[5] provides a unique opportunity to demonstrate electronic excitation transfer between identical molecules by a *direct chemical method of analysis*. Indeed, *(1)* may be considered as a stable, "masked" electronically excited acetone molecule. Irradiation of *(1)* in deuterioacetone, under conditions such that acetone[6] is not excited by direct absorption of light (high pressure Hg lamp, 365 nm line), effects the reaction scheme shown.

The acetone singlets and triplets generated from photolysis of *(1)* were trapped with dicyanoethylene and diethoxyethylene, respectively, to give the corresponding oxetanes *(2)* and *(4)*[7]. Since the excitation energy must originally reside on a $[H_6]$-acetone ($A—H_6$) molecule, one can determine the extent of energy transfer to $[D_6]$-acetone ($A—D_6$) by simply measuring the ratio of *(2)* to *(3)* and/or *(4)* to *(5)* in the reaction products.

The analysis of the reaction mixture was executed by a combination of gas chromatography and mass spectrometry. The relative amounts of *(2)* and *(3)*, or *(4)* and *(5)*, were determined from the intensities of the relevant masses (Table 1). As standard controls, authentic mixtures

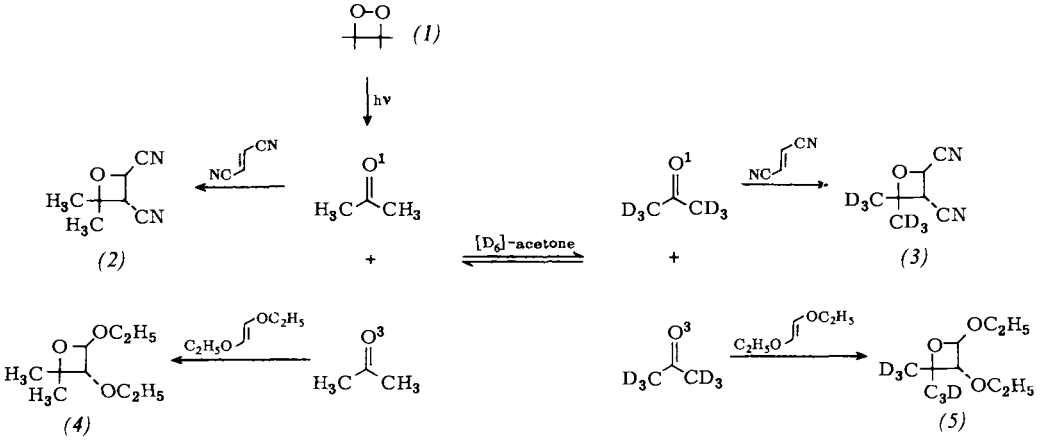

Fig. 1. Reaction scheme of energy transfer.

(Even if some anisotropy were involved in the reaction, say, initiated by excitation with polarized light, the rapid rate of tumbling of molecules in fluid solution converts the system into an isotropic one much faster than most physical measurements can be made).

of *(2)* and *(3)* [or *(4)* and *(5)*] were prepared and analyzed.

Table 1. Mass numbers for analysis of deuterium contents [8].

Fragment X=H,D	Oxetane (2)	(3)	(4)	(5)
CX_3CO	43	46	43	46
CX_3COCX_3	58	64	58	64
$(CX_3)_2CCHCN$	81	86	—	—
$(CX_3)_2CCHOC_2H_5$	—	—	100	106
$(M-15)$	121	124	—	—

Analysis of the oxetanes from addition of singlet acetone to dicyanoethylene revealed $5 \pm 2\%$ deuteriooxetane *(3)*

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in the total oxetane mixture, while the corresponding deuterated oxetane *(5)* from addition of triplet acetone to diethoxyethylene accounted for $10 \pm 5\%$ of the total oxetane mixture.

Application of Stern-Volmer kinetics[9] leads to the following rate constants for energy transfer:

Singlet-Singlet: $k_q^1 = 3.5 \times 10^6\ mol^{-1}\ s^{-1}$
Triplet-Triplet: $k_q^3 = 2.8 \times 10^6\ mol^{-1}\ s^{-1}$

Thus, within the experimental error of $\pm 50\%$, the two energy transfer rate constants are equal and about three orders of magnitude smaller than the value for diffusion in acetone ($\approx 5 \times 10^9\ mol^{-1}\ s^{-1}$).

$$A_1^* \curvearrowright A_2 \curvearrowright \ldots\ A_n \rightarrow A_1\ \ A_2\ \ldots \curvearrowright A_n^*$$

$$\Phi_{HOP} = \frac{k_q}{k_q + \sum k_d}[A] \qquad \begin{matrix} n^1 \approx 1 \\ n^3 \approx 14 \end{matrix}$$

The number of energy hopping events, Φ_{HOP}, depends on the ratio of the rates of hopping to the sum of all deactivation rates ($\sum k_d$). In pure acetone at room temperature ([A] = 14 M, $\sum k_d^1 \approx 0.6 \times 10^9\ s^{-1}$, $\sum k_d^3 \approx 2 \times 10^5\ s^{-1}$)[10] the singlet makes only one hop per lifetime, while the triplet makes about 14 hops per lifetime.

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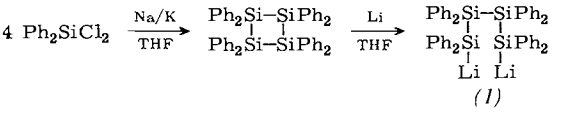
Boracyclopentasilane, a New Type of Heterocyclic Silane

By *Edwin Hengge* and *Dieter Wolfer*[*]

Only a few heterocyclic silanes with cumulated Si—Si bonds are known[1] and most of them contain, as hetero atoms, elements of the fourth, fifth and sixth main Group. Analogous cyclosilane derivatives with elements of the third main Group have so far been unknown. We here report the first synthesis of a boracyclosilane.

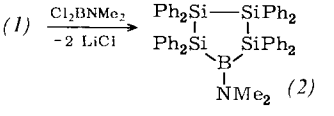
It is known that octaphenylcyclotetrasilane[2] reacts with lithium with ring fission to 1,4-dilithiooctaphenyltetrasilane *(1)*[3]:



(1)

We have been able to isolate this Li compound *(1)* as tetrahydrofuran adduct; it had previously been obtained only in solution and used therein for manifold reactions. Metalating ring cleavage in a little tetrahydrofuran leads to $Ph_8Si_4Li_2 \cdot 2THF$ being precipitated as yellowish-red, small crystals which can be recrystallized from cyclohexane: m.p. 121—123 °C (uncorr. in a sealed tube). ^{1}H-NMR (in C_6D_6): Ph multiplet at 3.25—2.08 ppm, two THF multiplets at 8.78 (THF in C_6D_6 8.47) and 6.68 (6.64) ppm. The compound is very sensitive to oxygen and hydrolysis.

First attempts to convert *(1)* by dichloro(phenyl)borane into nonaphenylboracyclopentasilane failed; we obtained only polymeric products. However, analogously to the work of *Nöth et al.*[4] who raised the electron density of a Si—B bond by dimethylamino-substitution, thus stabilizing it, it proved possible to cyclize *(1)* to 1-(dimethylamino)-2,2,3,3,4,4,5,5-octaphenyl-1-boracyclopentasilane *(2)* by means of dichloro(dimethylamino)borane:



(2)

The boracyclosilane *(2)* forms small white crystals, has an unusually low density, and is very sensitive to oxygen and hydrolysis; it is slightly soluble in benzene, toluene or xylene, still less so in cyclohexane and insoluble in pentane or ether. M.p. 261—263 °C (uncorr. in a sealed tube).

The ^{1}H-NMR spectrum (in C_6D_6; TMS standard) shows a singlet for the methyl-protons at 7.08 ppm and a phenyl multiplet at 3.16—2.17 ppm in the proportions 1 : 6.9 (calc. 1 : 6.7). In the IR spectrum the phenyl and dimethylamino vibrations are at their usual frequencies, but the νB—N at 1392 cm^{-2} lies remarkably low. In the Raman spectrum νB—N appears at 1394 cm^{-1} and a further band at 541 cm^{-1} which is presumably to be considered as a symmetrical ring vibration. The UV spectrum, compared with those of other heterocycles of the type Si_4X (with X = Si, Ge, N, P, O or S), gives a band at the particularly long-wave position 330 nm ($\varepsilon = 1700$).

Experimental

Solutions of $(Ph_2Si)_4Li_2 \cdot 2THF$ (0.044 mol) in THF (180 ml) and of Me_2NBCl_2 (0.044 mol) in benzene (250 ml)

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[1] See, *inter alia: E. Hengge* and *U. Brychcy*, Monatsh. Chem. *97*, 1309 (1966); *U. Wannagat* and *O. Brandstätter, ibid. 94*, 1090 (1963); *97*, 1352 (1966); Angew. Chem. *75*, 345 (1963); Angew. Chem. internat. Edit. *2*, 263 (1963); *M. Kumada et al.*, Kogyo Kagaku Zasshi *66*, 637 (1963); Chem. Abstr. *1963*, 15303.

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are added dropwise from two dropping funnels during 3 h into vigorously stirred anhydrous benzene (1000 ml) at 5 °C. LiCl is removed from the reaction mixture by filtration at room temperature. The benzene solution is concentrated and the product *(2)* is then precipiated by cyclohexane at 5 °C. All operations are effected under N_2. Crude yield 37%; after six-fold recrystallization from dry cyclohexane 26%.

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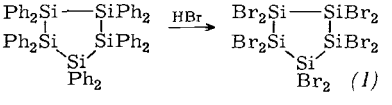
Cyclopentasilane, the First Unsubstituted Cyclic Silicon Hydride

By *Edwin Hengge* and *Günther Bauer*[*]

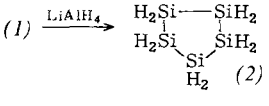
Only a few derivatives of cyclosilanes have previously been known and, except for a single chloro-derivative of uncertain structure[2], these all contained alkyl or aryl substituents[1]. Cyclic silanes containing functional groups were first obtained by removing phenyl groups from perphenylated cyclosilanes by means of HI[3], but this is not generally possible and led, for example, only to derivatives of pentaphenylcyclopentasilane $Si_5(C_6H_5)_5X_5$[4].

We have now found that decaphenylcyclopentasilane is converted quantitatively into decabromocyclopentasilane *(1)* by anhydrous HBr in a bomb tube at room temperature:



Compound *(1)*, easily prepared in this way and the first bromocyclosilane to be known, forms colorless crystals melting at 195 °C and extremely sensitive to moisture. The relative molecular masses (ebullioscopically, in benzene; mean of several measurements) are 939 (calc. 939.5). The Raman and IR spectra have very few lines, as expected; a Raman-active breathing vibration of the ring is observed at 510 cm^{-1} as well as the Si—Br bands.

As regards the reactions of *(1)* we were naturally most interested in the possibility of hydrogenation to the unsubstituted cyclosilane. This can be done by using very pure ethereal $LiAlH_4$ solution which should be added slowly to a benzene solution of the bromocyclosilane. After removal of the solvent a product could be isolated from the residue under reduced pressure (yield 80%); this proved to be the long sought cyclopentasilane *(2)*:



Si_5H_{10} is a colorless liquid with an extrapolated boiling point of ≈ 130 °C. Elemental analysis shows only silicon and hydrogen in the correct proportions. The ^{1}H-NMR spectrum (in benzene, internal standard benzene) shows a single sharp singlet at 6.57 ppm with a coupling constant J^{29}SiH of 195 Hz. The vibration spectra show few lines: IR: νSiH 2130, δSiH_2 865, 890 cm^{-1}; Raman: νSiH 2135, δSiH_2 891, 924, ring pulsation (ν_sSiSi) 382, ν_{as}SiSi 463, δ_{ring} 175 cm^{-1}. A theoretical estimate of the pulsation frequency, on the assumption that the ring is planar and with the nuclear separations and force constants of disilane, gave a value of 373 cm^{-1}[5].

The mass spectrum of *(2)* contains lines in the region of *m/e* 150 (molecular ion), 118 (Si_4 units with varying proportions of hydrogen), 88 (Si_3 units with varying proportions of hydrogen) and 60 (Si_2 units with varying proportions of hydrogen). The individual groups were split by isotope effects, as expected.

The existence of the cyclic silane C_5H_{10} can be regarded as proved by the findings described above.

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[5] We thank Dr. *F. Höfler* for calculating the pulsation frequency and for the vibration spectroscopic studies.

Crystal and Molecular Structure of $NH_4[S_4N_5O]$—A New Sulfur-Nitrogen Cage[1]

By *Ralf Steudel*, *Peter Luger*, and *Hans Bradaczek*[*]

$NH_4[S_4N_5O]$ *(1)* is obtained as yellow water-soluble crystals on reaction of $SOCl_2$ with liquid NH_3 and subsequent hydrolysis of the reaction products[2]. As the IR and mass spectrum of this compound indicate an unusual cage structure of the anion $S_4N_5O^-$, we have carried out a single-crystal X-ray structure analysis of *(1)*.

The compound crystallizes in the monoclinic space group $C\,2/m$ with $a = 17.848$, $b = 6.232$, $c = 7.095$ Å; $\beta = 104.83°$; $Z = 4$; $d_{exp.} = 1.96$, $d_{calc.} = 2.01$ g/cm^3. 1207 reflections were measured on an automatic Siemens single-crystal diffractometer with θ between 2.4° and 30°. 82 reflections whose intensities were less than twice the statistical error were treated as unobserved. The structure was solved by the multisolution method and refined by the method of least squares. Temperature factors of the atoms S, N and O were anisotropic, but that of the H atom was isotropically refined. Because the linear absorption coefficient was small and the crystal form was nearly that of a cube, we did not apply an absorption correction. After convergence of the refinements the final *R* value amounted to 5.1%. Figure 1 shows the result of the analysis; Table 1 lists the most important intramolecular distances and angles. Two neighboring ions NH_4^+ and $S_4N_5O^-$, joined by an O—H hydrogen bridge are placed on a common mirror plane. Both ions have C_s symmetry; moreover, the NH_4^+ ion is bonded to the N^2 atoms of two further anions by way of two N—H hydrogen bridges. Only one of the four H atoms of NH_4^+ does not take part in an H bridge.

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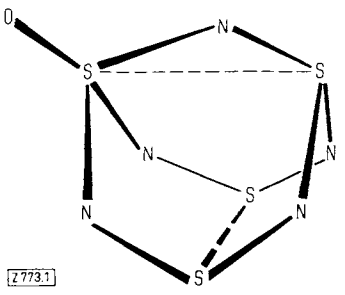
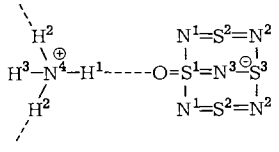


Fig. 1. Structure of the anion $S_4N_5O^-$.

Thus the cation is not tetrahedral but instead is strongly deformed (three different N—H nuclear separations, HNH angles between 82 and 128°).



The structure of the anion can be formally derived from the cage of S_4N_4[3], one S atom (S^1) carrying an O atom and bridged to a neighboring S atom (S^3) through an N atom. This oxidized S atom is almost tetrahedrally coordinated. The S=O nuclear separation, 1.433 Å, corresponds to that in other molecules with S=O double bonds (SO_3 1.42 Å; SOF_4 1.42 Å).

The formation of *(1)* from $SOCl_2$ and NH_3 can be interpreted by a series of successive condensations with elimination of HCl, H_2O and NH_3:

$$2\,SOCl_2 + 7\,NH_3 \xrightarrow{NH_3} HN(SONH_2)_2 + 4\,NH_4Cl$$

$$2\,HN(SONH_2)_2 \xrightarrow{H_2O} NH_4[S_4N_5O] + 3\,H_2O$$

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Lithium Derivatives of Silanol and Related Compounds

By *Stephen Cradock, Evelyn A. V. Ebsworth, Hans Moretto, David W. H. Rankin,* and *W. John Savage*[*]

Although disilylphosphane is relatively stable *in vacuo*, silanethiol and silaneselenol are not, while silanol is not known[1]. Alkali metal derivatives of these compounds are therefore difficult to obtain directly.

We find that methyllithium reacts smoothly in diethyl ether over a period of minutes at 227 K with $(SiH_3)_2Y$ (Y = O, S, Se)[2] or $(SiH_3)_3Z$ (Z = P, As); methylsilane is evolved in about 90% of the amount required by the equations:

$$(SiH_3)_2Y + CH_3Li \rightarrow Li[YSiH_3] + CH_3SiH_3$$

$$(SiH_3)_3Z + CH_3Li \rightarrow Li[Z(SiH_3)_2] + CH_3SiH_3$$

Table 1. Bond lengths and angles in $NH_4[S_4N_5O]$ *(1)*. Standard deviations in parenthesis.

Bond lengths [Å]					
N^4—H^1	1.03 (0.06)	S^1—O	1.433 (0.004)	S^2—S^2	2.633 (0.001)
N^4—H^2	0.98 (0.06)	S^1—N^3	1.580 (0.004)	S^1—S^3	2.717 (0.002)
N^4—H^3	0.93 (0.12)	S^1—N^1	1.591 (0.003)	S^1—S^2	2.658 (0.001)
N^2...H^2	2.00 (0.06)	S^2—N^1	1.631 (0.004)	S^2—S^3	2.741 (0.001)
O ...H^1	1.95 (0.06)	S^2—N^2	1.603 (0.003)	N^1—N^2	2.676 (0.004)
		S^3—N^2	1.651 (0.004)	N^1—N^1	2.524 (0.004)
		S^3—N^3	1.658 (0.005)	N^2—N^2	2.506 (0.005)
Bond angles [°]					
OS^1N^3	108.7 (0.2)	$N^1S^2N^2$	111.7 (0.2)	$H^1N^4H^2$	119 (5)
OS^1N^1	110.4 (0.2)	$S^2N^2S^3$	114.8 (0.2)	$H^1N^4H^3$	85 (7)
$N^1S^1N^3$	111.2 (0.1)	$S^1N^3S^3$	114.1 (0.3)	$H^2N^4H^2$	82 (5)
$N^1S^1N^1$	105.0 (0.2)	$N^3S^3N^2$	107.5 (0.2)	$H^2N^4H^3$	128 (5)
$S^1N^1S^2$	111.2 (0.2)	$N^2S^3N^2$	98.8 (0.2)		

The S—N nuclear separations in $S_4N_5O^-$ are somewhat more strongly differentiated than in S_4N_4, where they vary only between 1.596 and 1.634 Å. Nevertheless one must assume largely delocalized π-bonds within the S_4N_5 skeleton. The structural formula above can therefore be described only as a limiting structure.

As in S_4N_4, the contacts between the S atoms of one cage, being 2.7 Å, are appreciably smaller than the van der Waals S—S separations which are 3.7 Å. The smallest distances between different anions are practically in agreement with the van der Waals distances.

The lithium derivatives may be isolated as white crystalline solids by evaporation of the solvent. They have been characterized by their Raman spectra (obtained from solids and from solutions—Tables 1 and 2).

Table 1. Raman spectra (cm^{-1}) of lithium silyl sulfide and lithium silyl selenide $Li[YSiH_3]$ in diethyl ether.

Y = S	Y = Se	Assignment
2130 m, p	2118 m, p	ν_sSiH
945 w (br), dp	940 w (br), dp	δSiH_3
655 vw (br), dp	624 vw (br), dp	ρSiH_3
565 s, p	429 vs, p	νSi—Y

[1] Part 19 of Sulfur-Oxygen Compounds.—Part 18: *R. Steudel* and *M. Rebsch*, Angew. Chem. *84*, 344 (1972); Angew. Chem. internat. Edit. *11*, 302 (1972).

[2] *R. Steudel*, Z. Naturforsch. *24b*, 934 (1969).

[3] *B. D. Sharma* and *J. Donohue*, Acta Crystallogr. *16*, 891 (1963).

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Table 2. Raman spectra (cm^{-1}) of lithium disilyl phosphide and lithium disilyl arsenide $Li[Z(SiH_3)_2]$ in diethyl ether.

Z=P	Z=As	Assignment
2105 m, p	2110 m, p	$\nu_s SiH$
940 w (br), dp	930 m (br), dp	δSiH_3
635 vw (br), dp	580 w (br), dp	ρSiH_3
495 m, dp	—	$\nu_{as} Si_2Z$
470 s, p	374 vs, p	$\nu_s Si_2Z$
145 w, p?	122 w, p?	δSi_2Z

The ^{1}H-NMR spectra in general give the expected single Si*H* resonance, with satellites due to ^{29}Si in natural abundance [$^1J(^{29}SiH) \approx 200$ Hz in all cases]; we have shown by heteronuclear decoupling that in $Li(YSiH_3)$ the ^{29}Si spectrum is the expected quartet of sharp lines, whereas in $Li[Z(SiH_3)_2]$ the ^{29}Si spectrum is a quartet of quartets, the smaller splitting arising from ^3J(SiH). When Z=P, the main Si*H* resonance appears as a doublet at room temperature [^2J(PH)=15.5 Hz] and heteronuclear decoupling shows that the ^{31}P spectrum is a heptet. When Y=Se, satellites due to ^{77}Se appear at low temperatures [^2J(SeH)=11 Hz]; they collapse at temperatures above 273 K, presumably because of some exchange process, but at 253 K the ^{77}Se spectrum is a quartet.

Solutions of $Li(SSiH_3)$ and of $Li(SeSiH_3)$ react with trimethylchlorosilane to form $H_3SiSSi(CH_3)_3$ and $H_3SiSeSi(CH_3)_3$ respectively, which were characterized by their vibrational spectra. We are exploring further the synthetic potential of the lithium salts.

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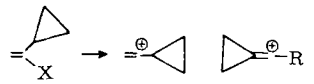
[1] *C. Glidewell, D. W. H. Rankin,* and *G. M. Sheldrick,* Trans. Faraday Soc. *65*, 1409 (1969).

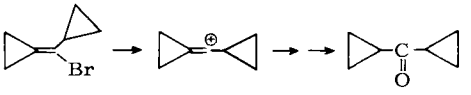
[2] *S. Cradock, E. A. V. Ebsworth,* and *H. F. Jessep,* J. C. S. Dalton *1972*, 359.

(3), whereas the corresponding open-chain model compounds react very slowly or not at all even in the presence of silver salts. If the β-carbon atom of the vinyl compound is itself part of a cyclopropane ring, then a reactive system is again obtained which affords the vinyl cation *(4)* by ionization[5]. Owing to their rigid geometry, cations of structure *(4)* are characterized by particularly favorable conditions for overlap between the vacant p-orbital and the cyclopropane bonds[5].



(1), X = Cl *(3)* *(4)*
(2), X = I

We have been able to combine the stabilizing effects of two cyclopropane rings. We synthesized (1-bromo-1-cyclopropylmethylene)cyclopropane *(5)*; the vinyl cation *(6)* derived therefrom is remarkably stable, as was shown by the rates of hydrolysis of *(5)* and product analysis.



(5) *(6)* *(7)*

The kinetics of solvolysis of *(5)* were determined for 50% and 80% ethanolic solutions at several temperatures and pH values (Table 1)[6]. The main product (>80%) of solvolysis was dicyclopropyl ketone *(7)*.

The data in Table 1 show conclusively that solvolysis of *(5)* occurs by an S_N1 mechanism and thus involves the intermediate vinyl cation *(6)*:*(5)* reacts faster in a solvent of higher ionizing power; the Winstein-Grunwald *m* value[7] of 0.89 (determined from the rate constants

Table 1. Rate of solvolysis of *(5)* in aqueous ethanol.

Ethanol concn. [%]	T[°C]	pH	$10^3 k$ [s^{-1}]	$\Delta H^{\neq}$ [kcal/mol]	$\Delta S^{\neq}$ [cal $mol^{-1} deg^{-1}$]
50	29.90±0.21	6.50	0.232±0.002	20.0	− 7.1
	48.76±0.12	6.50	1.82 ±0.03		
	67.30±0.05	6.50	9.94 ±0.02		
	67.35±0.08	8.00	10.3 ±0.04		
	67.34±0.08	9.30	11.0 ±0.007		
	100.0 [a]		146		
80	48.80±0.10	6.50	0.0619±0.0003	21.0	−10.7
	74.41±0.14	6.50	0.744 ±0.008		

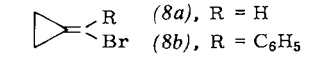
[a] Extrapolated.

Synthesis and Solvolysis of (1-Bromo-1-cyclopropylmethylene)cyclopropane: A Particularly Stable Vinyl Cation[1][**]

By *William E. Heyd* and *Michael Hanack*[*]

Formation of vinyl cations on solvolysis of vinyl halides is particularly favored by cyclopropyl groups in the α-position[2]; for example, the chloride *(1)*[3] and the iodide *(2)*[4] are readily solvolyzed to the intermediate cation at 48.80 and 48.76 °C) is one of the highest yet found for solvolysis of vinyl halides[2].

The special additional stabilizing effect of the cyclopropane ring in *(6)* is shown by comparison of the relative rates of solvolysis of *(5)* and the vinyl bromides *(8a)* and *(8b)* (80% ethanol, 100 °C[1,5]): *(8a)* $k_{rel}=1$; *(8b)* $k_{rel}=3.6\times10^3$; *(5)* $k_{rel}=1.51\times10^5$.



(8a), R = H
(8b), R = C_6H_5

The high stability of *(6)* is shown also by the fact that it has almost no tendency to rearrange. Whereas solvolysis

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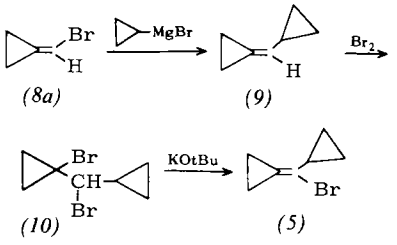
of *(8a)* affords exclusively the rearranged cyclobutanone[5], the main product in our case is dicyclopropyl ketone *(7)*.



For preparation of (1-bromo-1-cyclopropylmethylene)cyclopropane *(5)*, (1-bromomethylene)cyclopropane *(8a)*[5] was coupled with cyclopropylmagnesium bromide in THF in the presence of $FeCl_3$[8], yielding the hydrocarbon *(9)* which was then brominated in pentane at -70 °C. The resulting dibromide *(10)* was allowed to react with potassium *tert*-butoxide in dimethyl sulfoxide without further purification and the product *(5)* was isolated by preparative gas chromatography. NMR (CCl_4): $\tau = 8.30$ (1H/m, tertiary H); 8.72 (4H/AA'BB', methylenecyclopropane ring-protons); 9.12 (4H/m, cyclopropyl protons); IR (film): 1760 cm^{-1} (*exo*-methylenecyclopropane double bond); mass spectrum: $m/e = 172$, 174.

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4-Substituted Quinuclidinium Perchlorates as Models for the Determination of Polar Substituent Effects

By *Cyril A. Grob, Werner Simon*, and *Dieter Treffert*[*]

Because of their structure and high symmetry 4-substituted quinuclidines are particularly suitable for the quantitative measurement of polar substituent effects by pK_a measurements[1,2]. Now that this type of compounds has become considerably more accessible[3], measurements can be carried out on a broader basis. Table 1 lists the pK_a values of some 4-substituted quinuclidinium perchlorates *(1)* and, for comparison, those of their 3-substituted analogs *(2)*[4].

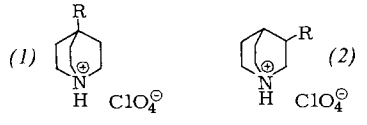

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Table 1. pK_a values of 4- and 3-substituted quinuclidinium perchlorates *(1)* and *(2)*, respectively, in water at 25 °C. Mean deviation from the mean value ±0.3%.

R	*(1)* pK_a	*(2)* pK_a
$C(CH_3)_3$	11.07	11.02
$CH(CH_3)_2$	11.02	—
H	10.96	10.96
C_2H_5	10.95	10.94
CH_3	10.88	10.91
$COCH_3$	9.45	9.67
$COOC_2H_5$	9.44	9.40
CN	8.07	7.81

The following conclusions can be drawn from the values in the Table:

a) The range of pK_a values measured for the salts *(1)* of the 4-series is wide and covers three pK_a units.

b) The differences in the pK_a values of the alkyl derivatives are significant, albeit small, in both the 4- *(1)* and the 3-series *(2)*. The electron-repelling +I effect increases in the expected order $CH_3 < C_2H_5 < (CH_3)_2CH < (CH_3)_3C$.

c) A methyl group in the 4- or the 3-position is electron-attracting relative to hydrogen. Within experimental error, the ethyl group is equal to hydrogen.

d) The fact that the acetyl group is more electron-attracting in the 4-position than in the 3-position confirms the superiority of the field model of the inductive effect[5,6]. The direct distance and the orientation of the substituent dipole with respect to the nitrogen atom are clearly decisive, and not the chain length.

Between 15 and 35 °C the differences between the pK_a values of quinuclidinium perchlorate and those of its 4-methyl and 4-isopropyl derivatives remain almost constant. Thus, the 4-substituent contributes to the free enthalpy of dissociation by way of the enthalpy term[7].

The pK_a values of the 4-substituted quinuclidinium perchlorates *(1)* show a linear correlation with *Taft*'s polar substituent constants σ^*[8] (correlation coefficient $r = 0.9978$), provided that hydrogen is excluded. The particular position of the pK_a value of hydrogen [cf. c)] is not yet understood. It therefore seems advisable to use 4-methylquinuclidinium perchlorate as the basis for a linear free-energy relation of the form

$$pK_a^{(CH_3)} - pK_a^{(R)} = \rho\sigma$$

which is analogous to the *Hammett* equation.

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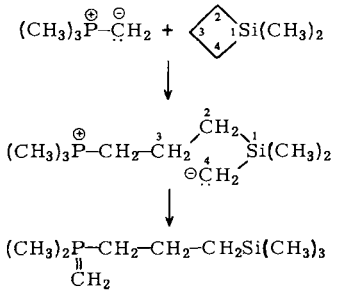
Abnormal Ring Opening of Silacyclobutanes by Trialkylalkylidenephosphoranes[1]

By *Hubert Schmidbaur* and *Walter Wolf*[*]

Present knowledge of the chemistry of silacyclobutanes[2] shows that both electrophilic[3] and nucleophilic ring-opening[4] affects only the Si—C bonds. Thus monosilacyclobutane rings are also usually opened at the "junction", *e.g.* by phenyllithium[4], and not with C—C bond cleavage. The same applies to carbene insertion by organomercury compounds[5], though the reaction is then accompanied by C—H insertion.

Attempts to silylate phosphorus ylides by silacyclobutanes revealed that the ylidic carbanion groups unexpectedly attack the strained ring system at the *C atom in position 3*. Heterolysis of the C—C bond occurs, yielding a new carbanion attached to silicon which then undergoes stabilization by prototropy to give a new phosphorus ylide. In this way dimethylmethylene[(3-trimethylsilyl)-*n*-propyl]phosphorane *(1)* is formed in almost quantitative yield from trimethylmethylenephosphorane[6] and 1,1-dimethylsilacyclobutane[2] in diethyl ether at $-10\,^{\circ}C$.

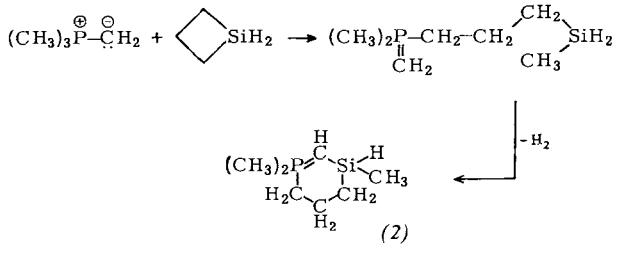
For well known reasons[7] one of the *P*-methyl groups loses a proton in the above-mentioned isomerization. *(1)*, b. p. 47 °C/0.1 torr, m. p. −10 °C, is unambiguously identifiable by analysis and spectroscopy. ^{1}H-NMR (neat, TMS ext.): $\delta CH_2{=}P$ 0.82, d, *J*(HCP) 7; δCH_3Si 0.12; δCH_3P −1.15, d, *J*(HCP) 12.5; δCH_2 at −0.48, −1.3, and −1.4 Hz ($A_2B_2M_2X$). Proton exchange induced by a trace of methanol causes $\delta CH_2{=}P$, δCH_3P, and δCH_2P (A_2) to collapse



to a common singlet; there then remain δCH_2 and δCH_2Si as the B_2M_2X portion which can be simplified to the B_2M_2 system by P-decoupling.

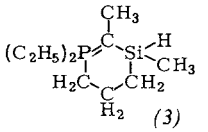
The abnormal course of the reaction is explained in terms of carbanion stabilization in the intermediate by the silicon atom. This possibility would not be provided by any alternative ring opening mode (attack at the 1- or 2-position).

When unsubstituted silacyclobutane is used, the analogous ring fission is followed by ring closure with extrusion of hydrogen.



The evolution of hydrogen is due to the presence of acidic phosphonium-hydrogen and negative *Si*-hydrogen functions in the same molecule in positions favorable to ring closure.

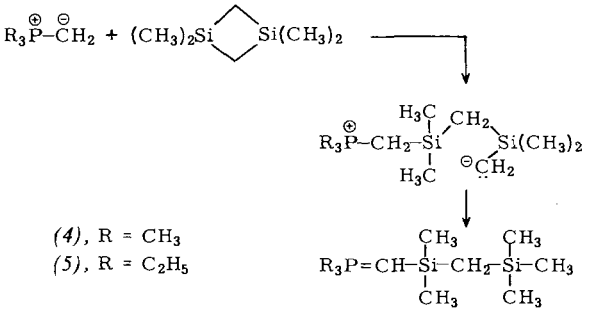
Reaction of $(C_2H_5)_3PCH_2$ and $(CH_2)_3SiH_2$ likewise affords the homologous heterocycle *(3)*. The two reactions occur rapidly and completely even at 0 °C. *(2)*, b. p. 46—47 °C/0.1 torr; ^{1}H-NMR (in C_6D_6, TMS ext.); δCH 1.2, d, J(*HCP*) 7.5; δCH_3Si −0.03, dd, *J*(*HCSiH*) 3, J(*HCSi*) 6.7, *J*(*HCSiCP*) 0.5; δCH_3P −1.13, d, J(*HCP*) 12 (broadened by the chirality center on Si); δHSi −7.73, dsex, *J*(*HSiCP*) 8.5; δCH_2 at −0.70, −1.73, and −2.63 Hz ($A_2B_2C_2X$); P-decoupling produces the expected changes. *(3)*, b. p. 63 °C/0.5 torr.



(3)

1,1,3,3-Tetramethyldisilacyclobutane is also easily cleaved by trialkylmethylenephosphoranes, but here there is no opportunity for alternative ring opening. Silylated ylides of types *(4)* and *(5)* are formed through Si—C cleavage.

In these cases nucleophilic attack on the hetero atom can also produce a stabilized carbanion, which then rearranges to the phosphorus ylide by proton abstraction from the PCH_2Si bridge[8,9].



(4), R = CH_3
(5), R = C_2H_5

That other nucleophilic reagents attack silacyclobutanes exclusively at the hetero atom is explained by the fact that in those cases the counter-ions present—*e.g.* Li^+ in the case of LiR—can assist by stabilizing the carbanion intermediate. Such assistance by counter-ions is absent in the case of salt-free ylides, and stabilization through the silicon atom therefore determines the course of the reaction.

Because of pronounced steric hindrance, reactions of triisopropylmethylenephosphorane[1] take place only slowly and incompletely. The nucleophilicity of methylenetriphenylphosphorane[10] no longer suffices for ring opening of disilacyclobutanes.

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Silylated Ylides as Components for Wittig Reactions[1, 2]

By *Hubert Schmidbaur* and *Herbert Stühler*[*]

From the few reported attempts to synthesize silylated olefins from carbonyl compounds and silylated ylides it is clear that Wittig olefin synthesis with these components does not proceed according to the usual scheme but leads to unexpected products[3, 4]. Complicated mechanisms are required to explain the generally complicated product distributions[3] and it is difficult to test their validity. Only in one case[5] did the reaction conform to the classical concept[6].

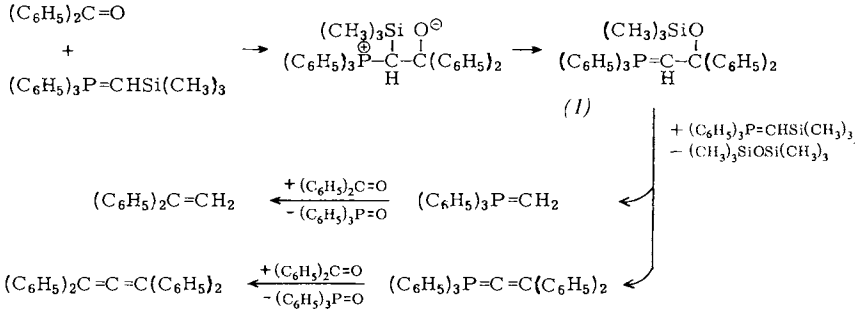
We have now found that calculable products are obtained only if the ylide and the carbonyl compound are used in the stoichiometric proportion 2:3 and if the ylide is pure and salt-free. These measures represent the only way of accommodating for the tendency to form a phosphane oxide as well as a disiloxane product.

The most important variants of the reaction course will be illustrated by three examples:

1. (Trimethylsilylmethylene)triphenylphosphorane[5, 7] and benzophenone afford tetraphenylallene and 1,1-diphenylethylene *quantitatively* along with triphenylphosphane oxide and hexamethyldisiloxane according to the following overall equation[3]:

$$3\,(C_6H_5)_2C{=}O + 2\,(C_6H_5)_3P{=}CHSi(CH_3)_3 \rightarrow$$
$$2\,(C_6H_5)_3PO + (CH_3)_3SiOSi(CH_3)_3$$
$$+ (C_6H_5)_2C{=}CH_2 + (C_6H_5)_2C{=}C{=}C(C_6H_5)_2$$

This result can be explained by a desilylation[8] of the second molecule of ylide by the primary product *(1)*; the $(C_6H_5)_3P{=}CH_2$ thus formed then reacts in the usual way:



2. On addition of $(C_6H_5)_2CO$ to $(CH_3)_3P{=}CHSi(CH_3)_3$[5, 9] the primary product *(2)* rearranges, after desilylation, by prototropy[10] in a different way, giving a *well defined phosphane oxide (3)*[11]:

$$3\,(C_6H_5)_2C{=}O + 2\,(CH_3)_3P{=}CHSi(CH_3)_3 \rightarrow$$
$$(CH_3)_3P{=}O + (CH_3)_3SiOSi(CH_3)_3$$
$$+ 2\,(C_6H_5)_2C{=}CH_2 + (CH_3)_2P(=O)CH{=}C(C_6H_5)_2$$
(3)

Mechanism:

$$(CH_3)_3P{=}C(H)-C(OSi(CH_3)_3)(C_6H_5)_2 \xrightarrow[-(CH_3)_3SiOSi(CH_3)_3]{+(CH_3)_3P=CHSi(CH_3)_3}$$
(2)

$$(CH_3)_3P{=}CH_2 + (CH_3)_2P(=CH_2)-CH{=}C(C_6H_5)_2$$
$$\downarrow (C_6H_5)_2C{=}O \qquad \downarrow (C_6H_5)_2C{=}O$$
$$(CH_3)_3P{=}O + (C_6H_5)_2C{=}CH_2 \quad (3) + (C_6H_5)_2C{=}CH_2$$

3. Similarly 2,4-dimethyl-1,3-pentadiene along with isobutene are formed from the last mentioned ylide and acetone:

$$3\,(CH_3)_2C{=}O + 2\,(CH_3)_3P{=}CHSi(CH_3)_3 \rightarrow$$
$$2\,(CH_3)_3PO + (CH_3)_3SiOSi(CH_3)_3$$
$$+ (CH_3)_2C{=}CH_2 + CH_3{-}C(CH_3){=}CH{-}C(CH_3){=}CH_2$$

A likely intermediate in this case is methallylidenetrimethylphosphorane. After desilylation, deprotonation occurs preferentially at one of the two methyl groups:

$$(CH_3)_3P{=}C(H)-C(OSi(CH_3)_3)(CH_3)_2 \xrightarrow[-\text{disiloxane}]{+\text{ylide}}$$

$$(CH_3)_3P{=}CH_2 + (CH_3)_3P{=}C(H)-C(CH_3){=}CH_2 \text{ etc.}$$

Reactions according to this new scheme make it possible to synthesize even complicated olefins under very mild

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conditions since the silyl group is an ideal protecting and leaving group for the ylides[12].

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[1] Organosilicon Chemistry of Phosphorus Ylides, Part 18.—Part 17: *H. Schmidbaur* and *W. Wolf*, Angew. Chem. *85*, 344 (1973); Angew. Chem. internat. Edit. *12*, 320 (1973).

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[11] *(3)*, m. p. 114—115 °C. ^{1}H-NMR (CH_2Cl_2): δCH_3 −1.27 (d, 6H) J(HCP) 13; δCH −6.42 (d, 1H), J(HCP) 15.5; δC_6H_5 −7.3 Hz (m, 10H). IR: ν(P=O) 1160 cm^{-1}. Relative molecular mass 240 (256.3).

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Low-temperature X-ray Structure Analysis of Ammonium Carbamate

By *Alfred Gieren*, *Walter Hoppe*, and *Klaus Fleischmann*[*]

We have carried out an X-ray structure analysis of ammonium carbamate ($NH_4^+CO_2NH_2^-$). Not only is this substance sensitive to moisture but also its relatively high volatility results in single crystals being unstable at room temperature even in dry air[1]. The analysis was therefore carried out in a low-temperature room at −50 °C while N_2 was used as protecting gas. The single crystals were obtained by passing CO_2 into liquid ammonia and then slowly evaporating the excess of ammonia.

Space group: *Pbca* with $a = 6.46$, $b = 6.66$, $c = 17.00$ Å; cell volume: 731.4 Å^3; $\rho_{exp}^{20\,°C} = 1.38$ g·cm^{-3}; $Z = 8$; $\rho_{calc.}^{-50\,°C} = 1.42$ g·cm^{-3}. The intensities were mostly measured photographically with a Weissenberg camera (oscillating procedure) but some few with a precession camera ($MO_{K\alpha}$ radiation). Evaluation afforded 1213 independent reflections (407 not observed).

The structure was solved by direct methods using the triple product rule and a program by *Hechtfischer*[2]. A Fourier synthesis calculated with the 300 largest, phased, unitary structure factors showed the positions of all the atoms (except H). Refinement, first with isotropic and then with anisotropic temperature factors, led to an R value of 10.5%.

The hydrogen atoms of the NH_2 group, but not those of the NH_4^+ group, could be seen after refinement in a difference Fourier synthesis. However, since the maxima were not sharp, these H positions were set in calculated positions (H1 parallel to C1—O2, H2 parallel to C1—O1, N—H = 1.0 Å) and only their temperature factors (isotropic) were included in the refinement ($R = 10.3\%$).

The planar carbamate ions associate to cyclic dimers (Fig. 1), which are held together by two N—H···O hydrogen bridges. The dimeric anion has a crystallographic symmetry

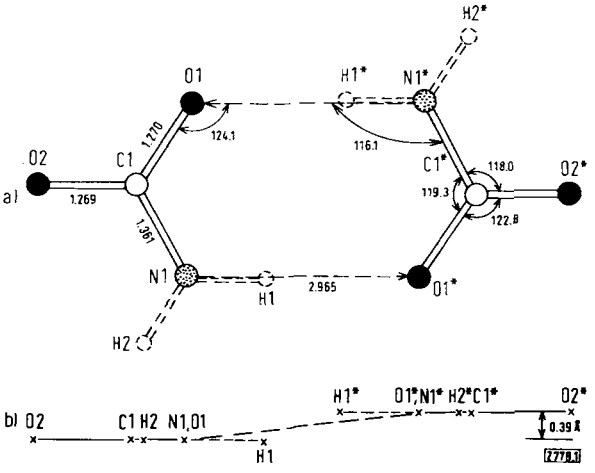

Fig. 1. Centrosymmetric dimeric anion in ammonium carbamate: a) Horizontal section: projection on N1, C1, O1; b) vertical section: projection along N1—O1. Standard deviations: 0.006 Å, 0.4°.

center. Its two portions are thus necessarily parallel but they do not lie strictly in one plane (separation of the two planes: 0.39 Å). HCO_3^- ions also form dimers in $KHCO_3$[3], but the anions in NH_4HCO_3[4] and $NaHCO_3$[5,6] and sodium sesquicarbonate ($Na_2CO_3 \cdot NaHCO_3 \cdot 2H_2O$)[7] polymerize—the latter with inclusion of H_2O molecules. Dimers of our type are found in, *e.g.* carboxylic acids and their amides[8]. Similar cyclic hydrogen bridges play a role in base-pairing of nucleic acids[9]. The N1—O1 hydrogen bridge is 2.96$_5$ Å long, which agrees well with the mean value of the N—H···O bridge (2.94 Å[8]) for acid amides. The hydrogen bridge is asymmetric but linear within a few degrees.

The C—N (1.36 Å) and the C—O distances (1.27 Å) do not differ significantly from those in urea[10] (1.356 ± 0.007 and 1.276 ± 0.008 Å, respectively); they reflect the expected double-bond character.

The dimeric anions form buckled layers parallel to (001). On their periphery lie the NH_4^+ ions, which, mainly by hydrogen bridges, cross-link both the layers and the dimeric anions within the layers. The NH_4^+ group has four nearest O neighbors at the corners of a distorted tetrahedron (N2···O2: 2.74, 2.80 Å; N2···O1, 2.80, 2.87 Å). A fifth oxygen atom (O2) is considerably further removed (3.11 Å) but still in the range of a N—H···O bridge, even if a long one. The second hydrogen atom (H2) of the amino-group also takes part in a weak H bridge (N1···O1: 3.37 Å). But, unlike the H bridges in the dimeric anion, the bridges just mentioned show large deviations from the ideal configuration. That the two C—O distances in the dimeric anion do not differ significantly is probably to be ascribed to the fact that both oxygen atoms act to about the same extent as acceptors for hydrogen atoms.

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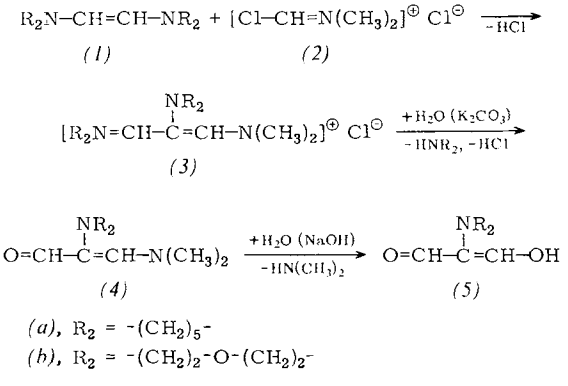
Vilsmeier Formylation of Enediamines[1]

By *Christian Reichardt* and *Klaus Schagerer*[*][**]

Whereas Vilsmeier formylation of enamines leads to formyl ketones and formyl aldehydes (dialdehydes)[2], the same reaction with enediamines should permit preparation of the hitherto inaccessible (dialkylamino)malondialdehydes.

If 1,2-dipiperidino- *(1a)* or 1,2-dimorpholino-ethylene *(1b)*[3] reacts with *N*-(chloromethylene)-*N*,*N*-dimethylammonium chloride *(2)* (produced from *N*,*N*-dimethylformamide and oxalyl chloride) in chloroform, then, after hydrolysis of the intermediate trimethinium salt *(3)*, the 2-(dialkylamino)-3-(dimethylamino)acroleins *(4)* can be isolated; their alkaline hydrolysis affords piperidino- *(5a)* and morpholino-malondialdehyde *(5b)*, respectively.



(a), R_2 = $-(CH_2)_5-$
(b), R_2 = $-(CH_2)_2-O-(CH_2)_2-$

The structures of all the new products were proved by elemental analysis and by IR, ^{1}H-NMR, and mass spectra.

The (dialkylamino)malondialdehydes *(5)* thus prepared for the first time are valuable starting materials for synthesis of dialkylamino-substituted polymethine dyes and heterocycles.

2-Piperidino-3-(dimethylamino)acrolein (4a)

Oxalyl chloride (21.6 g, 170 mmol) is added dropwise to a solution of *N*,*N*-dimethylformamide (11.9 g, 163 mmol) in chloroform (30 ml) with ice-cooling. Then a solution of 1,2-dipiperidinoethylene[3] (29 g, 150 mmol) in chloroform (30 ml) is added dropwise at −5 °C to the reaction mixture, which is next stirred for 12 h at room temperature and subsequently heated at 65 °C for 12 h. After cooling to 0 °C, this mixture is hydrolyzed first with ice-water (15 ml) and then with saturated potassium carbonate solution (180 ml) with subsequent heating at 70 °C for 2 h. Extraction with chloroform, removal of the solvent, and distillation of the residue in a high vacuum gave a forerun at 77 °C/0.03 torr, followed by the main fraction at 126 °C/0.03 torr, the latter solidifying to yellowish crystals in the receiver. Recrystallization from light petroleum (b. p. 40—60 °C) afforded colorless crystals (5.5 g, 20%) of m. p. 76—77 °C.—^{1}H-NMR ($CDCl_3$): 1.50 (m), 3.03 (m), 3.25 (s/CH_3), 6.35 (s/CH—N), and 8.78 ppm (s/CHO) (6:4:6:1:1).—Mass spectrum: $m/e = 182$ (M^+).

Piperidinomalondialdehyde (5a)

Compound *(4a)* (1.82 g, 10 mmol) and NaOH (0.5 g) in water (3 ml) were stirred together for 2 h at 100 °C. A little 1-propanol was added for homogenization and the pH was established at 4—5 by means of 2 N HCl. Extraction with ether, removal of the ether, and sublimation of the residue at 120 °C (bath temperature) and 0.1 torr yielded thin colorless crystals (0.99 g, 64%) of m. p. 195 °C—^{1}H-NMR ($CDCl_3$): 1.90 (m), 3.65 (m), 7.95 (s/OH), and 8.66 ppm (s/CH) (6:4:1:2).—Mass spectrum: $m/e = 155$ (M^+).

Morpholinomalondialdehyde *(5b)*, m. p. 205 °C (dec.), was obtained analogously.

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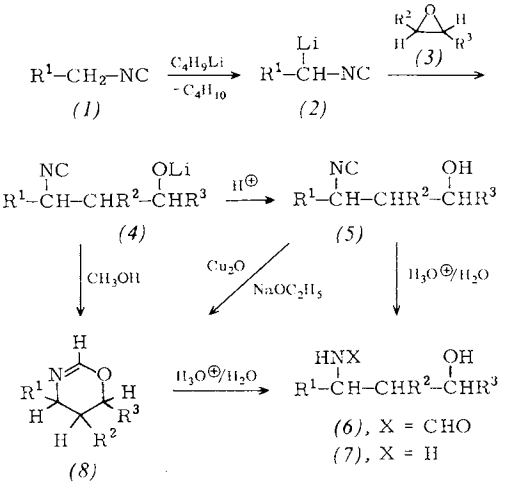
5,6-Dihydro-4*H*-1,3-oxazines and γ-Amino Alcohols from α-Metalated Isocyanides and Epoxides[1]

By *Ulrich Schöllkopf* and *Reinhard Jentsch*[*]

5,6-Dihydro-4*H*-1,3-oxazines *(8)* without a substituent at position 2 or γ-amino alcohols *(7)* deserve attention as precursors of tetrahydro-1,3-oxazines which are of interest chemotherapeutically[2] or as intermediates in syntheses. We have found that these compounds can be obtained simply and in relatively good yield by treating α-lithiated isocyanides *(2)* with epoxides *(3)*, although other routes[3] give only poor yields. Investigations so far have shown that unsymmetrically substituted epoxides are attacked preferentially or exclusively at the less hindered carbon atom. The lithium compounds *(2)* can be obtained from alkyl isocyanides *(1)* and butyllithium.



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The primary products *(4)* can be isolated as γ-isocyano alcohols by addition of one equivalent of glacial acetic acid. Depending upon the experimental conditions acid hydrolysis of these products yields, either γ-(formylamino) alcohols *(6)* or γ-amino alcohols *(7)*. 5,6-Dihydro-4*H*-1,3-oxazines are obtained by allowing ethanolic solutions of the primary adducts *(4)* or the γ-isocyano alcohols *(5)* containing sodium ethoxide to stand or by warming *(5)* with copper(I) oxide in benzene[4]. The γ-amino alcohols *(7)* or their *N*-formyl derivatives *(6)* can also be obtained from the dihydrooxazines *(8)* by acid hydrolysis.

residue is distilled (see Table 1 for b. p.). Characteristic IR bands (film): ν = 3500—3300 (OH), 2140—2150 (N≡C) cm^{-1}.

5,6-Dihydro-4H-1,3-oxazines (8)

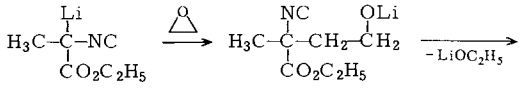
Compound *(5)* (40 mmol) is stirred for 2—12 h with copper(I) oxide (10 mg) in boiling benzene (50 ml) until the N≡C band disappears from the IR spectrum. The mixture is filtered and the filtrate is evaporated in a rotary evaporator (crude yield almost quantitative) and the residue is distilled, giving *(8)* (see Table 1 for b. p.). *(8)* are also

Table 1. γ-Isocyano alcohols *(5)*, 5,6-dihydro-4*H*-1,3-oxazines *(8)*, and γ-amino alcohols *(7)*.

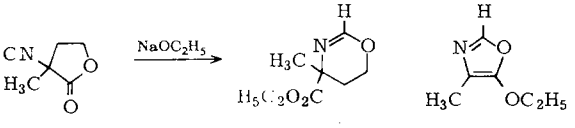
	R¹	R²	R³	Yield [%]	*(5)*, B. p. [°C/torr]	*(8)* [b], B. p. [°C/torr]	*(7)* [c], B. p. [°C/torr]
a	H	H	H	52	96–98/8	122–124/760	185–188/760 (105–110/10)
b	H	H	CH_3	78	101–103/11	63–65/60	115/11
c	H	H	C_6H_5	74	120–122/0.1	75–76/0.03	—
d	H	H	CH_2Cl	48	87–90/0.04	40/0.2	—
e	H	CH_3	CH_3	48	56–58/0.1	—	—
f	C_6H_5	H	H	80	100/0.02	70/0.2	—
g	C_6H_5	CH_3	CH_3	66	106–107/0.05 [a]	70/0.05 [a]	101–103/0.1 [a]
h	CH_3—O—$(CH_2)_2$	H	H	82	85–87/0.04	87–89/12	—
i	CH_3—O—$(CH_2)_2$	H	CH_3	76	85/0.05 [a]	40/0.1 [a]	
j	$(CH_3)_2N$—$(CH_2)_2$	H	C_6H_5	70	viscous oil [a]	115–123/0.1 [a]	—

[a] Possibly a mixture of diastereoisomers.
[b] Crude yield almost quantitative.
[c] Yield almost quantitative.

Ethyl 2-isocyano-2-lithiopropionate *(9)* and ethylene oxide afford 2-isocyano-2-methylbutyrolactone *(11)* as the first isolable product, presumably *via* the intermediate *(10)*. When treated with sodium ethoxide in ethanol, this lactone is converted into ethyl 5,6-dihydro-4-methyl-4*H*-1,3-oxazine-4-carboxylate *(12)*[5], which is the precursor of α-methylhomoserine. 5-Ethoxy-4-methyloxazole *(13)* is formed as by-product, resulting from intramolecular cyclization of *(9)*.



(9) *(10)*



(11) *(12)* *(13)*

γ-Isocyano alcohols (5)

Butyllithium (40 mmol, as a solution in pentane; precooled to *ca.* −70°) is added from a dropping funnel precooled by methanol/Dry Ice) over *ca.* 30 min to a solution of the isocyanide *(1)* (40 mmol) in tetrahydrofuran (50 ml) at −70 to −50 °C. To the resulting solution or suspension of *(2)* is added a solution of the epoxide *(3)* (40 mmol) in tetrahydrofuran (30 ml). The cooling bath is then removed and the mixture is stirred for *ca.* 10 min. at 0 °C, cooled again to −20 °C, and next treated with glacial acetic acid (40 mmol). The solvent is removed in a rotary evaporator, and the residue is shaken with water (20 ml) and methylene chloride (200 ml). The phases are separated and the aqueous phase is again extracted with methylene chloride (50 ml). The methylene chloride solutions are dried over magnesium sulfate and evaporated and the

obtained, although in lower yield, by carrying out the reaction *(2)* + *(3)* → *(4)*, adding methanol (30 ml) to the solution of *(4)* and stirring the whole at room temperature for 10 h. *(8)* are further obtained by keeping *(5)* at 40 °C in a solution of sodium (50 mg) in anhydrous ethanol (30 ml) for 4 h. Characteristic IR bands (film): ν = 3060—3080 (C—H), 1640—1650 (N=C), 1100—1150 (C—O—C); characteristic NMR signals (CCl_4): τ = 2.8—3.2 (d/H-2); $J_{H-2/H-4} \approx 2$ Hz).

γ-Amino alcohols (7) from (5) or (8)

Compounds *(5)* or *(8)* (20 mmol) are treated with 6 N hydrochloric acid (10 ml) with cooling, and the mixtures are stirred for 30 min at 50 °C. NaOH pellets (5 g) are added, and the *(7)* are extracted thrice with methylene chloride (50 ml portions). The methylene chloride solutions are dried over magnesium sulfate, the solvent is removed, and the residues are distilled; the yields of *(7)* are almost quantitative (see Table 1 for b. p.). *(7a)* can be distilled directly from the aqueous alkaline solution, without extraction.

γ-(Formylamino) alcohols (6)

Conversion of *(5)* into *(6)* can be effected as previously described[6].

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A [17]Annulenyl Anion[1][**]

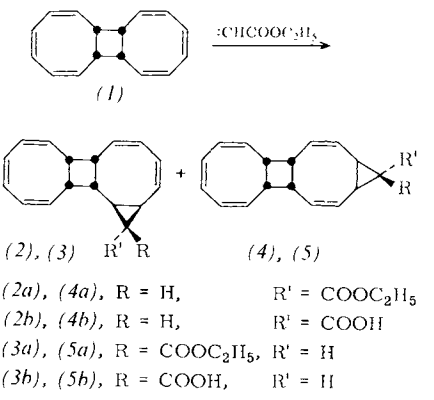
By *Gerhard Schröder*, *Günter Plinke*, *Donald M. Smith*, and *Jean F. M. Oth*[*]

Of the vinylogs of the cyclopentadienyl anion or the [5]annulenyl anion that obey the Hückel rule, the all-*cis*-[2] and the *cis,cis,cis,trans*-[9]annulenyl anion[3] have so far been reported. Also, one relatively complicated derivative each of the [17]-[4a] and [13]-annulenyl anion[4b] have been described. The aromatic character of these compounds has been convincingly proved by, *inter alia*, their ^{1}H-NMR spectra.

Now we report the synthesis and some properties of the [17]annulenyl anion, $C_{17}H_{17}^{\ominus}$, *(8)*. A suitable starting material is dimeric cyclooctatetraene *(1)*, m.p. 53 °C[5], which with diazoacetic ester in presence of copper powder at 100 °C yields the liquid adducts *(2a)*, *(3a)*, *(4a)*, and *(5a)*.

Repeated dry column chromatography (SiO_2) affords *(2a)* and *(3a)* and an inseparable mixture of *(4a)* and *(5a)* (see Table 1).

The positions of the three-membered ring and the ester group relative to the cyclobutane-protons in *(2a)*, *(3a)*, and *(4a)*/*(5a)* were determined by, *inter alia*, the paramagnetic shifts of individual proton resonance signals in the presence of europium tris(tetramethylheptanedionate). Of the crystalline acids formed on hydrolysis of *(2a)*, *(3a)*, and *(4a)*/*(5a)*, recrystallization afforded *(2b)*, *(3b)*, and *(5b)* in the pure state (see Table 1).



Photolysis of *(2a)*, *(2b)*, *(3b)*, and *(5b)* in ether at −80 °C by means of a low-pressure UV lamp led to the monosubstituted cycloheptadecaoctaenes *(6)* (having unknown configuration). In this way a red liquid *(6a)*, which according to thin-layer chromatography is homogeneous, is obtained from *(2a)*; the ester group is on the sp^3-hybridized C atom ($\bar{\nu}_{C=O}$ = 1735 cm^{-1}, 1H at τ = 5.5). The red liquid *(6b)* is formed from each of *(2b)*, *(3b)*, and *(5b)*, but nothing can be said about their homogeneity. Here too

Table 1. Data for compounds *(2)*—*(5)*.

Cpd. [6]	Yield [%] [a]	M.p. [°C]	^{1}H-NMR, τ [ppm] [b]	UV, λ [nm] (ε) [c]
(2a)	≈11	liquid	3.9–4.8 (10H/several m) 5.96 (2H/q; J = 7 Hz) 6.65 (3H/pseudo-d) 7.8–8.3 (3H/m) 8.8 (3H/t; J = 7 Hz) (1H/m)	228 (6700) sh 258 (2300) sh
(2b)		195–196	−1.9 (1H/s) 3.9–4.8 (10H/several m) 6.7 (3H/m) 8.05 (3H/m) 8.9 (1H/t, J = 4.5 Hz)	228 (8000) sh 258 (2200)
(3a)	≈3	liquid	3.9–4.7 (10H/several m) 5.95 (2H/q; J = 7 Hz) 6.65 (3H/pseudo-d) 7.4 (1H/m) 8.15 (3H/m) 8.76 (3H/t; J = 7 Hz)	228 (6700) sh 258 (2300) sh
(3b)		199	3.0 (1H/broad s) 3.9–4.7 (10H/several m) 6.7 (3H/pseudo-d) 7.3 (1H/m) 8.2 (3H/m)	228 (7300) sh 258 (1900)
(4a)/*(5a)*	≈6	liquid	3.9–4.9 (10H/several m) 5.95 (2H/2q; J = 7 Hz) 6.2–7.5 (4H/several m) 7.6–9 (6H, 3H at 8.8/2t; J = 7 Hz)	258 (2000) sh
(5b)		205	−0.5 (1H/s) 4.3 (10H/m) 6.35 (2H/m) 6.65 (2H/m) 7.85 (2H/d; J = 5 Hz) 8.63 (1H/t; J = 5 Hz)	250 (2000)

[a] Referred to the amount of *(1)* used.
[b] 60 MHz spectrum, *(4a)*, *(2b)*, *(3a)*, *(4a)*/*(5a)* in CS_2, *(3b)* in D_8-THF, *(5b)* in CCl_4.
[c] In ether.

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the carboxyl group is attached to the saturated C atom ($\tilde{\nu}_{C=O} = 1710\,cm^{-1}$). No isomerization with hydrogen shift has yet been observed for compounds *(6)*.

Surprisingly, *(6b)* decomposes smoothly in acetone at 20 °C to CO_2 and cycloheptadecaoctaene which can be separated into a crystalline and a liquid fraction by column chromatography (SiO_2, pentane) and fractional crystallization from pentane. For *crystalline* $C_{17}H_{18}$ (m.p. 126 °C) we propose structure *(7)*. Spectral comparison indicates that the *liquid* component is identical with a $C_{17}H_{18}$ that we had previously obtained by a somewhat different route[7] (see Table 2).

of relative intensities 2:2:1. The difference between the chemical shifts of the inner (high field) and the outer protons (low field) amounts to *ca.* 17 ppm. We therefore describe *(8)* as aromatic. Hydrolysis regenerates *(7)*.

When equimolar amounts of *(7)* and cyclopentadienylpotassium react in D_8-THF, then according to the NMR spectrum an equilibrium is set up containing *ca.* 80% of *(8)* and cyclopentadiene. However, an excess of KOH in D_8-THF is required for formation of *(8)* from *(7)* to be visible by NMR spectroscopy. The acidity of *(7)* is thus of the same order of magnitude as that of cyclopentadiene or water.

Table 2. Data for compounds *(7)*, liquid $C_{17}H_{18}$ and *(8)*.

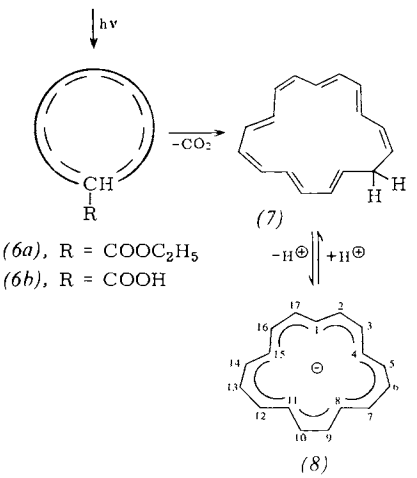
Cpd.	Yield [%]	M.p. [°C]	^{1}H-NMR, τ [ppm]	UV, λ_{max} [nm] (ε)
(7) [6]	≈32 [a] ≈90 [b]	126	2.5–3.5 (3 H/m) 3.6–4.7 (13 H/m) 7.1 (2 H/pseudo-t, $J \approx 5$ Hz) [e]	225 (16000) 260 (27000) 276 (30000) 365 (3800) [g]
$C_{17}H_{18}$ [6]	≈ 4 [a] ≈40 [c]	liquid	4.0 (16 H/m with flanks falling to 2.0 and to 4.9) 6.4–7.4 (2 H/m) [e]	225 (14000) 260 (26000) 276 (28000) 362 (3500) [g]
(8) counterion $Li^{\oplus}$	≈80 [d]		0.48 (10 outer H/m) 1.79 (H-6, H-13/t; $J = 9.5$ Hz) 17.97 (5 inner H/m) [f]	295 (53000) 426 (36000) 447 (210000) 580 (2400) 616 (2500) 673 (7700) [h]

[b] Referred to *(8)*.
[c] Referred to the methylene adduct of *(1)* [7].
[d] Referred to the amount of *(7)* used.
[e] 60 MHz spectrum in CS_2 with TMS as internal standard.
[f] 100 MHz spectrum, in D_8-THF with D-THF as internal standard; at −70 °C.
[g] In ether.
[h] In ether at −70 °C.

On catalytic hydrogenation, *(7)* and the liquid $C_{17}H_{18}$ give cycloheptadecane [m.p. 63—65 °C (64—65 °C[18]), NMR in CCl_4: τ = 8.7 (s)].

A [17]annulenyl anion is smoothly formed on treatment of *(7)* or liquid $C_{17}H_{18}$ in D_8-THF at −78 °C with a base, *e.g.* *n*-butyl- or methyl-lithium and is optically recognizable by a color change from red to dark green. The NMR spectrum (see Table 2) is in full accord with structure *(8)* (C_{2v} symmetry). Irradiation at the frequency of the signal at τ = 0.48 simplifies the triplet at τ = 1.79 to a singlet and the band at τ = 17.97 to three singlets

(2a), (2b), (3b), (5b)



(6a), R = $COOC_2H_5$
(6b), R = COOH

(7)

(8)

The thermal stability of *(7)* and *(8)* is noteworthy: *(7)* in hexachlorobutadiene, and *(8)* [from *(7)* and *n*-butyllithium] in D_8-THF, remain substantially unchanged on one hour's heating at 100 °C[19].

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[1] Annulenes, Part 18.—Part 17: *G. Schröder, G. Heil, H. Röttele,* and *J. F. M. Oth*, Angew. Chem. *84*, 474 (1972); Angew. Chem. internat. Edit. *11*, 426 (1972).

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[6] Molecular weights (mass-spectroscopic) and, for *(2b)*, *(3b)*, *(5b)*, and *(7)* satisfactory C,H analytical results are available.

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[8] *L. Ruzicka, W. Brugger, M. Pfeiffer, H. Schinz*, and *M. Stoll*, Helv. Chim. Acta 9, 499 (1926).

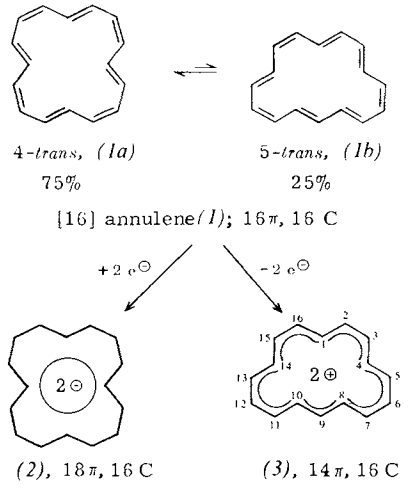
[9] The structure *(7)* proposed is based on two assumptions: a) that protonation of *(8)* occurs with the minimum of structural changes, and b) that electrocyclic reactions in a hexatriene segment containing a central *cis*-double bond of cycloheptadecaoctaene [there are two such segments in *(7)*] may not, according to model considerations, lead to relatively strain-free bi- or poly-cyclic valence isomers. Assumption b) explains the thermal stability of *(7)*.

A [16]Annulenediyl Dication[1][**]

By *Jean F. M. Oth, Donald M. Smith, Uwe Prange*, and *Gerhard Schröder*[*]

Neutral [4*n*]annulenes ($C_{4n}H_{4n}$, $n=1$, 2, 3, *etc.*) can in principle be converted in two ways into species that obey the Hückel rule [$(4n\pm2)$ π-electrons], namely a) by acceptance (reduction) and b) by loss (oxidation) of two electrons. Examples of case a) are the [8]-[2], [12]-[3], and [16]-annulenediyl dianions *(2)*[4]. No example of case b), *i.e.* formation of a dication from a [4*n*]annulene, has yet been reported[5].

We here report a surprisingly simple synthesis of a [16]annulenediyl dication *(3)* from [16]annulene *(1)*[6].



It was originally our intention to arrive at a homo[15]annulenyl cation *(5)* by proton addition to *(1)*, in analogy to the protonation of cyclooctatetraene which leads to the homotropylium ion *(4)*[7]. When FSO_3H (or FSO_3D) acts on red *(1)* in SO_2/CD_2Cl_2 at *ca.* −80 °C—a reaction that is accompanied by formation of varying amounts of polymer—there is a color change from red to violet and production of a species whose ^1H- and ^{13}C-NMR spectra (see Fig. 1) are in agreement only with those of the [16]annulenediyl dication *(3)*.

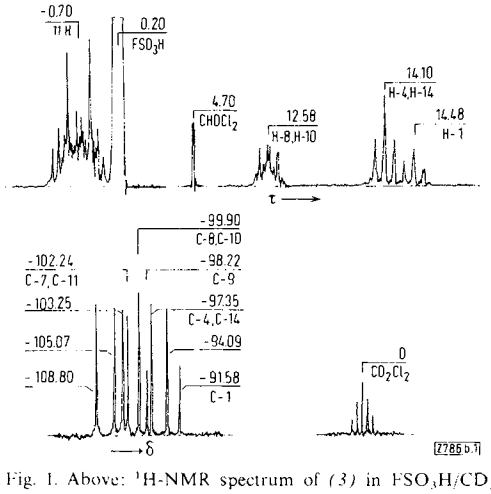


Fig. 1. Above: ^1H-NMR spectrum of *(3)* in $FSO_3H/CD_2Cl_2/SO_2$ at −25 °C and 100 MHz. Below: ^{13}C-NMR spectrum of *(3)* after heteronuclear broad-band decoupling in $FSO_3H/CD_2Cl_2/SO_2$ at −60 °C and 25 MHz. Internal standard: methylene dichloride [8].

The following arguments prove the existence of the dication *(3)*:

1. Neither the ^1H- nor the ^{13}C-NMR spectrum contains a signal that could be ascribed to a methylene group of a homo[15]annulenyl cation, *e.g. (5)*. For more detailed information the ^{13}C-NMR spectrum of *(4)* was measured (see Fig. 2). The signal of the methylene carbon atom of *(4)* appeared at +12.20 ppm.

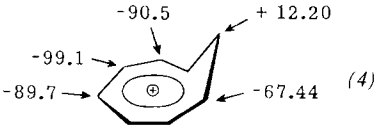
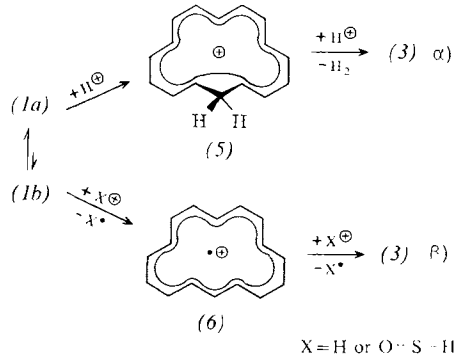


Fig. 2. ^{13}C-NMR data for *(4)* in $FSO_3H.CD_2Cl_2/SO_2$ at −60 °C and 25 MHz. Internal standard: CD_2Cl_2 [8]. δ-values are shown.

2. The ^1H-NMR spectrum indicates that the magnetic field in *(3)* induces a diamagnetic ring current: five inner protons appear at high field, and eleven outer ones at low field; the two triplets at $\tau=14.10$ (2H) and 14.48 (1H) ($J=12.5$ Hz), which we assign to the protons H-4/H-14 and H-1, respectively, also prove a system with cyclic delocalized π-bonds. The complex triplet at $\tau=12.58$ (2H) is the X part of an AA'BXX' system. Finally, the signals for the inner protons simplify to three singlets on irradiation at the absorption band at $\tau=-0.70$.

3. The center of gravity of the nine ^{13}C-absorption signals of *(3)* lies at $\delta=-100.7$ ppm with CD_2Cl_2 as standard (or at $\delta=-24.7$ with benzene as standard). The former value lies exactly on the straight line obtained when the ^{13}C signals of monocyclic neutral or charged aromatic compounds are plotted against the corresponding electron density per C atom[9].

4. The relative intensities of the ^{13}C signals (2:2:2:2:2:1:2:2:1) proves a structure with C_{2v} symmetry. The individual ^{13}C signals were assigned by selective ^1H-decoupling.



At least two possibilities can be discussed for formation of *(3)* from *(1)*[10]. By route α) a homo[15]annulenyl cation *(5)* is first formed, and subsequent protonation of a C—H bond of the methylene group can bring about production of *(3)* with loss of H_2. In route β) the proton or the conjugate acid of sulfur dioxide ($OSOH^{\oplus}$) acts as oxidizing agent, and the radical cation *(6)* is thus an intermediate. In α) molecular hydrogen is formed, but

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[**] We thank Badische Anilin- und Soda-Fabrik AG for the cyclooctatetraene.

in β) (X=H) elemental hydrogen. It proved impossible to detect hydrogen gas during formation of *(3)* in spite of a careful search.

Attempts to trap *(3)* by $NaOAc/CH_3OH$ have so far led only to indefinite polymeric products.

We plan to convert *(1)* into *(5)* by weaker acids and in other solvents, as well as to oxidize *(1)* electrochemically.

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[1] Annulenes, Part 19.—Part 18: *G. Schröder, G. Plinke, D. M. Smith,* and *J. F. M. Oth*, Angew. Chem. *85*, 350 (1973); Angew. Chem. internat. Edit. *12*, 325 (1973).

[2] *T. J. Katz*, J. Amer. Chem. Soc. *82*, 3785 (1960); *T. Schaefer* and *W. G. Schneider*, Can. J. Chem. *41*, 966 (1963).

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[5] Of the annulenediyl dications, only the tetramethyl derivative of the cyclobutadienyl dication was previously known. It was obtained by treatment of 3,4-dichloro-1,2,3,4-tetramethylcyclobutene with SbF_5 in SO_2 or SO_2ClF: *G. A. Olah, J. M. Bollinger,* and *A. M. White*, J. Amer. Chem. Soc. *91*, 3667 (1969).

[6] a) *G. Schröder* and *J. F. M. Oth*, Tetrahedron Lett. *1966*, 4083; *J. F. M. Oth* and *J.-M. Gilles, ibid. 1968*, 6259. b) In solution there is a dynamic equilibrium between the 4-*trans*-*(1a)*, 75%, and the 5-*trans*-configuration *(1b)*, 25%, of *(1)* [6a].

[7] *J. L. von Rosenberg, J. E. Mahler,* and *R. Pettit*, J. Amer. Chem. Soc. *84*, 2842 (1962); *S. Winstein, H. D. Kaesz, C. G. Kreiter,* and *E. C. Friedrich, ibid. 87*, 3267 (1965).

[8] δ is defined as follows: $\delta = 10^6 \times (\nu_0 - \nu)/\nu_0$, where ν_0 is the resonance frequency of the standard and ν is the resonance frequency of the observed signal at the same field strength H_0: *J. A. Pople, W. G. Schneider,* and *H. J. Bernstein:* High-Resolution Nuclear Magnetic Resonance. McGraw-Hill, New York 1959.

[9] *H. Spiesecke* and *W. G. Schneider*, Tetrahedron Lett. *1961*, 468.

[10] a) It has long been known that polycondensed aromatic compounds are oxidized by strong acids and, *inter alia*, by superacids, *via* radical cations to dications: *D. M. Brouwer* and *J. A. van Doorn*, Rec. Trav. Chim. Pays-Bas, *91*, 1110 (1972), who give further references. b) Heptafulvalene can be oxidized to the ditropylium ion: *H. Volz* and *M. Volz-de Lecea*, Liebigs Ann. Chem. *750*, 136 (1971), who cite further references.

An Aza[13]annulene[1][**]

By *Gerhard Schröder, Günter Frank,* and *Jean F. M. Oth*[*]

Oxa- and aza-[13]annulenes are isoelectronic with the aromatic [14]annulene[2]. They belong to the group of higher-membered heteroannulenes (C_nH_nX, *e.g.* $n=8$, X=O or NR[3], or $n=16$, X=O or NR[4]). For several reasons, *e.g.* π-electron structure and intramolecular rearrangements, this class of compound has been studied for

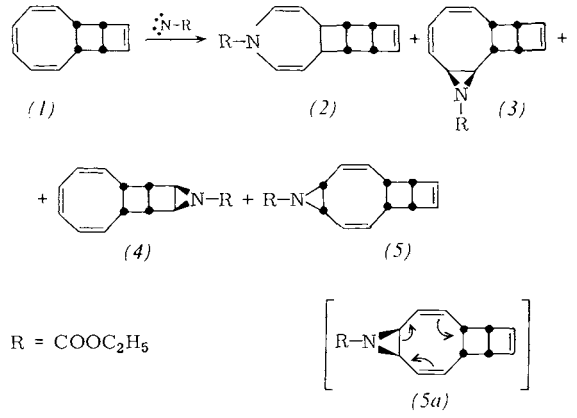

Table 1. Data for compounds *(2)*—*(5)*.

Cpd. [8]	Yield [a] [%]	M.p. [°C]	^{1}H-NMR, τ [ppm] [b]	UV, λ [nm] (ε) [c]
(2)	≈7	69–70	3.25 (2H/pseudo-d; J=10 Hz) 3.48 (2H/narrow m) 5.31 (2H/pseudo-d; J=10 Hz) 5.75 (2H/q; J=7 Hz) 6.60, 6.92, 7.52 (each 2H/one m each) 8.66 (3H/t; J=7 Hz)	231 (19000)
(3)	≈22	liquid	3.50 (2H/m) 3.90–4.80 (4H/m) 5.92 (2H/q; J=7 Hz) 6.54 (3H/m) 7.03 (1H/m) 7.55 (2H/m) 8.74 (3H/t; J=7 Hz)	225 (4000) sh
(4)	≈13	73	4.21 (6H/m) 5.90 (2H/q; J=7 Hz) 6.37 (2H/m) 6.67 (2H/pseudo-d) 7.15 (2H/m) 8.75 (3H/t; J=7 Hz)	253 (1500)
(5)	≈5.2	68	3.67 (2H/narrow m) 4.57 (4H/pseudo-s) 5.95 (2H/q; J=7 Hz) 6.21 (2H/m) 6.67 (2H/m) 7.03 (2H/pseudo-s) 8.75 (3H/t; J=7 Hz)	end absorption only

[a] Referred to the amount of *(1)* used.
[b] 60 MHz spectrum, in CCl_4, with TMS as internal standard.
[c] In methanol.

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[**] We thank the Badische Anilin- und Soda-Fabrik for the cyclooctatetraene.

several years past[3-5]. We here report the synthesis and properties of an *N*-(ethoxycarbonyl)aza[13]annulene *(8)*.

The tricyclic hydrocarbon $C_{12}H_{12}$ *(1)*[6] reacts with *N*-(ethoxycarbonyl)nitrene [from *N*-(*p*-nitrobenzenesulfonyloxy)urethane and triethylamine[7]] in CH_2Cl_2 at 10—20 °C, yielding the adducts *(2)*—*(5)* which can be separated and obtained pure by repeated dry column chromatography (SiO_2; pentane/ether 30:1 to 4:1) and recrystallization (Table 1) [the numbering *(2)*—*(5)* follows the order of retention volume on column chromatography].

and a brilliant yellow crystalline constitutional isomer of *(6)* to which we provisionally assign structure *(7)*, this being in accord with the NMR and UV spectra (see Table 2) and with the IR spectrum (in CS_2; *no* carbonyl band at 1700 cm^{-1}; bands of medium strength at 1750, 1645, 1285, 1045, 1000, and 750 cm^{-1}; strong absorption at 1200 cm^{-1}).

Irradiation of *(4)* affords a yellow oil (50—60% after chromatography) which could be crystallized from a little methanol. This yellow crystalline compound is an

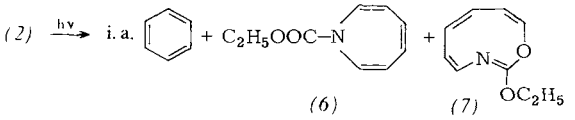
Table 2. Data for compounds *(7)*, *(8)*, and *(9)*.

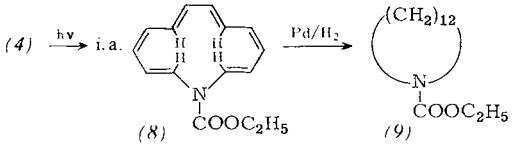
Cpd. [8]	Yield [%]	M.p. [°C]	^{1}H-NMR, τ [ppm]	UV, λ [nm] (ε)
(7)	≈3.5 [a]	96—97	2.75 (2H/narrow m) 3.70 (4H/m) 5.75 (2H/q; J=7Hz) 8.68 (3H/t; J=7Hz) [b]	300 (34000) [c]
(8)	≈25 [d]	78 (decomp.)	3.1–4.3 (8H/m) 5.0 (2H/m) 5.45 (2H m) 5.80 (2H/q with further splitting J=7Hz) 8.70 (3H/t with further splitting J=7Hz) [e]	213 (18000) 275 (33000) 345 (7000) [f]
(9)	≈95 [g]	liquid	5.96 (2H/q; J=7Hz) 6.81 (4H/pseudo-t; J=6.5Hz) 8.59 (20H/pseudo-s) 8.78 (3H t; J=7Hz, partly obscured [h]	

[a] Referred to the amount of *(2)* used.
[b] 100 MHz spectrum, in CCl_4 with TMS as internal standard.
[c] In methanol.
[d] Referred to the amount of *(4)* used.
[e] 100 MHz spectrum, in CS_2 with TMS as internal standard at −60 °C.
[f] In cyclohexane.
[g] Referred to the amount of *(8)* or mother-liquor residue.
[h] 60 MHz spectrum, in CCl_4, with TMS as internal standard.

The NMR spectra indicate that *(3)* is an asymmetric molecule but that *(2)*, *(4)*, and *(5)* have a plane of symmetry. If the addition of *N*-(ethoxycarbonyl)nitrene occurs analogously to epoxidation[9], the aziridine ring in *(3)* and *(4)* is *syn* and in *(5)* is *anti* to the cyclobutyl protons. The formation of *(5a)* with the *syn*-arrangement of the three-membered ring is demonstrable only indirectly through *(2)*. *(2)* is formed from *(5a)* by a Cope rearrangement as shown by the arrows[10].

The chromophoric seven-membered ring system in *(2)* and the eight-membered ring system in *(4)* are suitable for photolysis, and this was carried out with *ca.* 500 mg each of *(2)* and *(4)* in *ca.* 1.2 l of ether at −70 °C by means of a low-pressure UV lamp. Working up and purification were by chromatography (−10 to 0 °C, pentane/ether), and subsequent recrystallization. From *(2)* we isolated benzene (*ca.* 90%), *N*-(ethoxycarbonyl)azepine *(6)*[11] (*ca.* 45%), an unidentified yellow liquid (*ca.* 3%),





aza[13]annulene to which we assign configuration *(8)*, this proposal being based on the assumption that the two multiplets at τ=5.0 and 5.45 are indicative of four inner protons and thus of four *trans*-double bonds [see Table 2 for the data pertinent to *(8)*].

In the range 40 to −60 °C the NMR spectrum of *(8)* shows only slight temperature-dependence of the olefinic proton signals. Below 0 °C the quartet and triplet of the methylene and methyl protons, respectively, undergo at least a doubling with different intensities[12], which appears to indicate the presence of various conformers.

The residue in the mother liquor from crystallization of *(8)* is oily and yellow and, according to thin-layer chromatography, contains only one component; its NMR spectrum shows, alongside traces of *(8)*, only absorptions for olefinic (τ=3.1—4.4) and ethyl protons (τ=5.75 and 8.7). Catalytic hydrogenation (Pd/C) of both *(8)* and the residue from the mother liquor yields the same liquid monocyclic urethane *(9)* (see Table 2). *(8)* is unusually sensitive to air and in solution is thermally moderately stable; changes in the NMR spectrum become evident after 1 hour's heating at 50 °C. We are currently occupied in elucidating the structures of the rearrangement products.

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[1] Annulenes, Part 20.—Part 19: *J. F. M. Oth, D. M. Smith, U. Prange,* and *G. Schröder*, Angew. Chem. *85*, 352 (1973); Angew. Chem. internat. Edit. *12*, 328 (1973).

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[5] *F. Sondheimer*, Accounts Chem. Res. *5*, 82 (1972).

[6] *G. Schröder* and *W. Martin*, Angew. Chem. *78*, 117 (1966); Angew. Chem. internat. Edit. *5*, 130 (1966).

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[8] The compounds gave satisfactory values on C,H analysis and mass spectroscopic determination of molecular weight.

[9] *G. Plinke* and *W. Henne*, unpublished work.

[10] Precursors of this rearrangement are known; see, *e.g.*, *S. Masamune* and *N. T. Castellucci*, Angew. Chem. *76*, 569 (1964); Angew. Chem. internat. Edit. *3*, 582 (1964); *A. G. Anastassiou*, *S. W. Eachus*, *R. L. Elliot*, and *E. Yakali*, Chem. Commun. *1972*, 531; and [4a].

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[12] Similar observations have been made for a) *N*-(ethoxycarbonyl)-aza[17]- and -aza[9]annulene: a) *G. Schröder*, *H. Röttele*, and *J. F. M. Oth*, unpublished work; b) *A. G. Anastassiou*, *R. P. Cellura*, and *J. H. Gebrian*, Chem. Commun. *1970*, 375; *K. Hojo* and *S. Masamune*, J. Amer. Chem. Soc. *92*, 6690 (1970).

A Macroisopolyanion of Molybdenum: $Mo_{36}O_{112}^{8-}$

By *Karl-Heinz Tytko*, *Bernd Schönfeld*, *Bruno Buss*, and *Oskar Glemser*[*]

In continuation of our study of the reactions occurring on acidification of molybdate or tungstate solutions[1] we have investigated a series of aqueous molybdate solutions ($c = 0.1$—1 M[2]) at increasing degrees of acidity Z[3]. With $Z \approx 1.8$, we have found a new, uniform, unusually large species, namely the macroisopolyanion $Mo_{36}O_{112}^{8-}$, to exist in both the solution and the solid state. To our knowledge, this is *the largest uniform discrete ion yet proved to exist in solution or to have been isolated as a salt in the solid state.* Our conclusion is based, as described below, on Raman-spectroscopic measurements, determination of molecular masses by ultracentrifugation, X-ray crystallography, and mathematical analysis of potentiometric equilibrium curves for the system H^+/MoO_4^{2-}, the mode of formation being:

$$36\,MoO_4^{2-} + 64\,H^+ \rightarrow Mo_{36}O_{112}^{8-} + 32\,H_2O$$

Raman spectrum[4]: Intensity difference diagrams[5] (Fig. 1) show that in the region $Z > 1.6$ there are two reactions, one of which is to be ascribed to the formation and the other to further reaction of a new uniform polymolybdate species with a formation maximum in the region $Z \approx 1.8$. These two reactions can also be recognized by the appearance of isosbestic points.

In the intensity difference diagram there is a sharp transition between the two straight lines along which the two reactions proceed; from the sharpness of the intersection, which corresponds to the formation maximum in the solution, we can estimate that the new polymolybdate species reaches a molybdenum fraction[7] of >0.95 and that the role of precursors and subsequent products is no longer

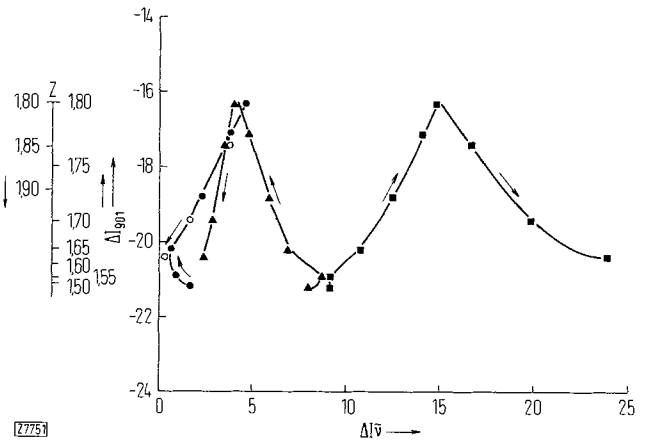

Fig. 1. Intensity difference diagram for the system H^+/MoO_4^{2-} ($c = 0.2$ M), relative to the MoO_4^{2-} spectrum in the region $Z > 1.5$ for three pairs of wave numbers: ■ 955/901, ▲ 971/901, ● ○ 983/901 cm^{-1}.

or not yet significant. The Raman spectrum of this solution (Fig. 2) can thus be regarded as identical with that of the new species in solution. Equilibration on formation of this species is complete after about 30 min at most and no further slower reaction follows.

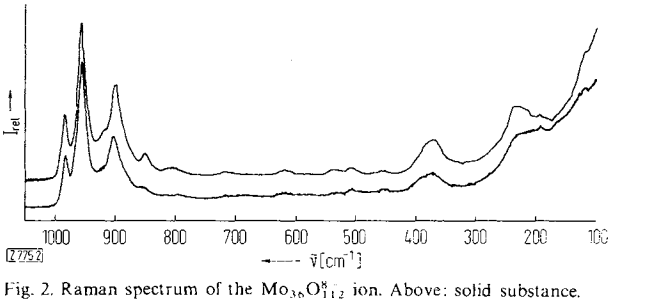

Fig. 2. Raman spectrum of the $Mo_{36}O_{112}^{8-}$ ion. Above: solid substance. Below: solution.

Crystallization of salts, which despite varying acid/base ratios (MoO_3/M_2O, where M = Na, K, NH_4, Ba/2), all give the same Raman spectrum identical with that of the solution (Fig. 2), occurs shortly after acidification from highly concentrated solutions having $Z \approx 1.8$ (the limiting concentration depends on the cation used). This proves that the solution and the crystalline solid both contain the same polymolybdate ion. Such behavior was previously found in the system H^+/MoO_4^{2-} only for the monomolybdate ion MoO_4^{2-} ($Z^+ = 0$[8]) and the 8,7-heptamolybdate ion $Mo_7O_{24}^{6-}$ ($Z^+ = 8/7 = 1.14$). A proof of this kind is very important for clarification of the mechanism of formation of polymetalate ions since results obtained on the solid (*e.g.* analysis or structure determination) thus can be used for statements about the thermodynamically most stable species in solution formed by a specific mechanism under defined conditions (degree of acidity, time, concentration)[9].

Analysis: Analysis of the salts gave the ratio Na/Mo = 0.20—0.22, K/Mo = 0.22—0.24 and NH_4/Mo =

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0.22–0.28. *Lindqvist*[10] had previously found a ratio Na/Mo = 0.23–0.29 for samples obtained by a method similar to ours, but without recognizing the nature of the species or, especially, its uniformity. The salts, which readily effloresce, contain a high proportion of water of crystallization, amounting to 2.2 H_2O/Mo, inclusive of any OH groups that may be present (they would be determined as H_2O).

The value of Z^+ derived from the above mentioned base/acid ratio amounts to 1.72—1.80, average 1.77. As we have explained, this value also applies to the new polymolybdate species in solution. The structure of the system H^+/MoO_4^{2-} in the region $Z > 1.6$ leads us to expect numerical agreement between the Z value of the solution at the formation maximum and the Z^+ value of the new polymolybdate.

Aggregation state: To determine the state of aggregation of the new polymolybdate species we have used the ultracentrifuge[17] and the sedimentation equilibrium procedure (schlieren optics) to measure the molecular masses in 0.2 M solutions at various degrees of acidity in the presence of 0.4 M Na(Cl) as inert electrolyte. We found a maximum at $Z \approx 1.8$ and determined for this in 0.1—0.2 M solutions an apparent molecular mass M_{app}[11] of ≈ 5620. Assuming that the species has a Z^+ value close to 1.8 and contains no OH group, the best approximation to the observed molecular mass would be a 38-molybdate ion $Mo_{38}O_{118}^{8-}$ ($Z^+ = 68/38 = 1.79$) with M = 5540. However, the uncertainties in the assumptions and the difference between M_{app} and M make it necessary to reckon with an error of about 5%. Control measurements on the heptamolybdate ion $Mo_7O_{24}^{6-}$ by a similar method of evaluation gave M_{app} about 10% too high. Thus aggregation states of 34—40 appear possible.

X-ray investigation: The sodium salt crystallizes in monoclinic prisms with space group $Cc—C_s^4$ or $C2/c—C_{2h}^6$ and the following lattice constants: $a = 40.2$; $b = 19.4$; $c = 33.4$ Å; $\beta = 139.2°$; $V = 16460(\pm 170)$ Å^3. In agreement with theoretical considerations of structure, the space groups exclude 34-, 35-, 37-, 38- and 39-molybdates. For a 36-molybdate the formula would be $Na_8Mo_{36}O_{112} \cdot 80H_2O$ ($Z^+ = 64/36 = 1.78$) and for a 40-molybdate $Na_8Mo_{40}O_{124} \cdot 88H_2O$ ($Z^+ = 72/40 = 1.80$). The density was determined pycnometrically (benzene or acetonitrile) as $d_{exp} = 2.72$ g/cm^3. The number of formula units in the unit cell is thus $z = 4$. For a 36-molybdate the calculated X-ray density is $d_{calc} = 2.77$ g/cm^3, and for a 40-molybdate is $d_{calc} = 3.06$ g/cm^3. If one assumes further that the O atoms are in closest spherical packing[12], as is found for all polymolybdates of known structure, one arrives at a packing density of 20.6 Å^3/O atom for a 36-molybdate and 18.7 Å^3/O atom for a 40-molybdate; the former value agrees very well with the packing densities of isopolymolybdates of known structure. The 40-molybdate is excluded by both these arguments. The new polymolybdate species is thus a 36-molybdate[14].

Structural considerations and a structural proposal: On the basis of our theoretical studies of the modes of formation and structures of polytungstate and polymolybdate ions[9], we can exclude the formation of such a large aggregate as a 36-molybdate ion by successive association of octahedron to octahedron. An 18-molybdate ion, which could dimerize to a 36-molybdate ion, is also too large to be built up in this way. Not till we reach the 12-molybdate ion, which could afford a 36-molybdate ion by trimerization, is formation by such a successive association of octahedra possible; however, structural considerations exclude any trimerization in principle (this would lead to structures of lower symmetry that would represent a section from a more symmetrical structure that could be obtained by tetramerization). The next possibility is tetramerization of four 9-molybdate ions which would lead to an ion with, in the ideal case, T_d symmetry (dimerization of two 9-molybdate ions to an 18-molybdate and dimerization thereof to the 36-ion is also conceivable). Fig. 3 shows a structure with a $Mo_{36}O_{112}$ skeleton built on this principle. In view of the terminal O atoms present and the pH range at which it exists, this species could take up at most approximately twelve negative charges and does not need to contain OH groups for structural reasons.

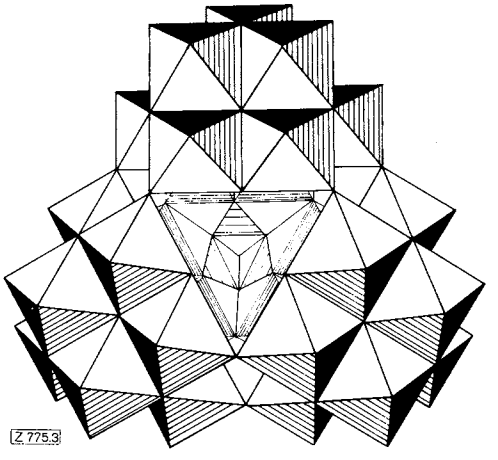

Fig. 3. Structure proposed for the $Mo_{36}O_{112}^{8-}$ ion.

It requires a minimum Z^+ value (no OH group) of 64/36 = 1.78, which affords a maximum charge of 8− and thus (charge $\lesssim 12-$) again it may not contain an OH group. The formula of the ion shown in Fig. 3 therefore is $Mo_{36}O_{112}^{8-}$ ($Z^+ = 64/36 = 1.78$).

Table 1. Overall formation constants β and standard deviation σ_Z for two sets of molybdate species according to EMF data of *Sasaki* and *Sillén*.
I: Set according to *Sasaki* and *Sillén*; II: Same set except species 64,36 in place of species 34,19.

Species	log β I	log β II
1,1	3.89	3.89
2,1	7.50	7.50
8,7	57.74	57.74
9,7	62.14	62.14
10,7	65.68	65.68
11,7	68.21	68.21
34,19	196.30	...
64,36	...	373.69
5,2	19	19
σ_Z [a]	0.0078	0.0089

[a] To prevent equalization of the σ_Z values, we used, for the calculation of σ_Z, only those runs in which a species 34,19 or 64,36 can occur, *i.e.* the runs for which data with $Z > 1.5$ were available.

Because of the symmetry (absence of a symmetry center) the four 36-molybdate ions per unit cell can be placed only on two-fold axes (the $\bar{4}$ tetrahedral axes coincide with the two-fold rotational axes). With the lattice constants given above each anion has six nearest neighbors

at a distance of *ca.* 16.5 A. The volume occupied by the anion in the direction of the six neighboring ions (determined on a model of the structure here proposed) is sufficiently small to avoid any overlap therewith. The macroisopolyanion takes four molecules of water of crystallization into its interior, while the remaining 76 molecules of water of crystallization fill the space between the anions.

Mathematical analysis of potentiometric equilibrium curves for the system H^+/MoO_4^{2-}: By a mathematical analysis of the $Z, \log h$[16] equilibrium curves for the system H^+/MoO_4^{2-}, *Sasaki* and *Sillén*[15] deduced for large values of Z the existence of a large anion of probable formula $Mo_{19}O_{59}^{4-}$ ($Z^+ = 34/19 = 1.79$). Using their data we have calculated that a set of species in which the 34,19-ion is replaced by a 64,36-ion would give only slightly less good standard deviation of Z (Table 1); and in this connection it should be noted that the calculations become increasingly better for the 64,36-ion as the concentration is increased. *Sasaki* and *Sillén*'s measurements thus do not run counter to the results of our investigations.

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[1] *O. Glemser, W. Holznagel, W. Höltje,* and *E. Schwarzmann,* Z. Naturforsch. *20b*, 725 (1965); *O. Glemser, W. Holznagel,* and *S. I. Ali, ibid. 20b*, 192 (1965); *O. Glemser* and *K. H. Tytko, ibid. 24b*, 648 (1969); *K. H. Tytko* and *O. Glemser, ibid. 25b*, 429 (1970).

[2] All the data for concentration, including those for the polymolybdate ions, refer to Mo. A solution of, *e.g.*, a species $Mo_7O_{24}^{6-}$ that is 1 M in this sense contains 1/7 mol of $Mo_7O_{24}^{6-}$ per l.

[3] By the degree of acidity Z of a solution is meant the molar ratio of *reacted* H^+ to MO_4^{2-} *applied initially*.

[4] Measurements were performed on a CODERG PH I Raman spectrometer combined with an OIP 181 E 200 mW-He-Ne-laser.

[5] If for a solution appropriate steps are taken to obtain linearity between the concentration of a species and the intensity of its Raman spectrum, intensity difference diagrams can be used in the same way as extinction difference diagrams in absorption spectroscopy [6] for clarification of the course of chemical reactions.

[6] *K. H. Tytko*, Dissertation, Technische Hochschule Aachen 1967; *H. Mauser*, Z. Naturforsch. *23b*, 1021, 1025 (1968).

[7] By "molybdenum fraction" we mean the amount of molybdenum, expressed as a fraction, in the species under discussion.

[8] By Z^+ value of an isopolyion we mean the ratio of the stoichiometric coefficients of H^+ and MO_4^{2-} in the overall equation of formation of the isopolyion.

[9] *K. H. Tytko* and *O. Glemser*, Chimia *23*, 494 (1969); Z. Naturforsch. *26b*, 659 (1971); *K. H. Tytko*, Angew. Chem. *83*, 935 (1971); Angew. Chem. internat. Edit. *10*, 860 (1971); Lecture at Heidelberg 1972, and at the 1st Meeting, International Society for the Study of Solute-Solute-Solvent Interactions, Marseille 1972.

[10] *I. Lindqvist*, Nova Acta Regiae Soc. Sci. Upsal. Series IV, *15*, No. 1 (1950).

[11] The apparent molecular masses M_{app} must be corrected in two respects in order to yield true molecular masses: M_{app} is to be extrapolated to $c = 0$ (this gives $(M_{app})_0$), and that value must be further corrected in respect of the charge.

[12] The Na^+ ions take part in the packing, analogously to ammonium polymetalates [13].

[13] *R. Allmann*, Acta Crystallogr. B *27*, 1393 (1971); *I. Böschen, B. Buss*, and *B. Krebs*, to be published.

[14] X-ray investigation of the Ba, Na, and NH_4 salts of the 36-molybdate ion gave a triclinic unit cell for the Ba salt. For the Na salt (the NH_4 salts are isotypic) several monoclinic species were found whose diffraction patterns were the same or very similar. Analogous calculations and considerations (see above and the structural proposal) lead to an almost identical distribution of the 36-molybdate ions in the unit cell. Further investigation is in progress.

[15] *Y. Sasaki, I. Lindqvist*, and *L. G. Sillén*, J. Inorg. Nucl. Chem. *9*, 93 (1959); *Y. Sasaki* and *L. G. Sillén*, Acta Chem. Scand. *18*, 1014 (1964); *Y. Sasaki* and *L. G. Sillén*, Ark. Kemi *29*, 253 (1968).

[16] $h = H^+$ concentration at equilibrium.

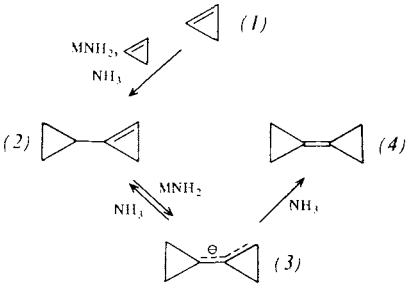
[17] We thank Dr. *W. Bähr*, MPI für Biophysikalische Chemie, Göttingen, for his help with this part of the investigation.

Eliminations from Three-Membered Rings: Cyclopropylcyclopropene and Bicyclopropylidene from 1-Chlorobicyclopropyl[**]

By *Lutz Fitjer* and *Jean-Marie Conia*[*]

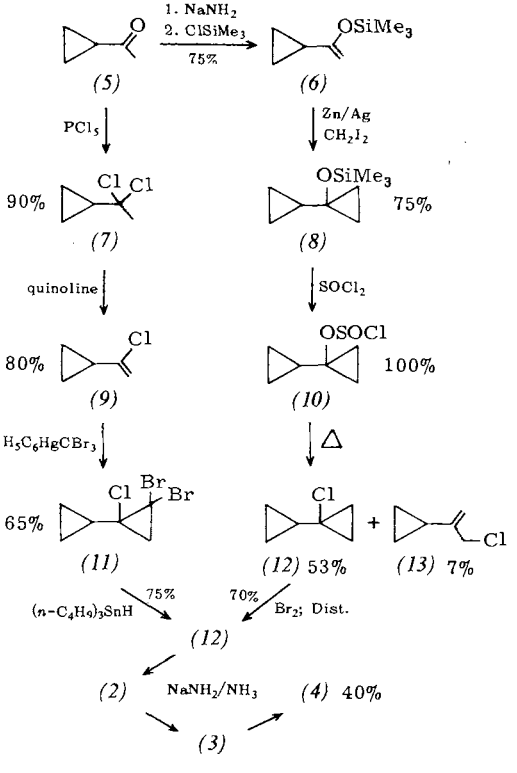
Bicyclopropylidene *(4)* has a key position in the chemistry of polycyclopropylidenes ([*n*]-rotanes)[1] as the direct precursor of tricyclopropylidene ([3]-rotane)[2] and tetracyclopropylidene ([4]-rotane)[3].

(4) can be obtained by cyclopropanation of dimethyleneallene[3] or by anionic dimerization of cyclopropene *(1)* by metal amides in liquid ammonia with subsequent isomerization of the cyclopropylcyclopropene *(2)* by way of the allylic anion *(3)*[4].



The preparative value of the isomerization of *(2)* to *(4)* remained, however, limited because of the poor availability of cyclopropene *(1)*[5] and the poor yield in the dimerization[4].

We have therefore tried to prepare *(2)* by elimination of hydrogen chloride from 1-chlorobicyclopropyl *(12)*.



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[**] This work was supported by the Deutsche Forschungsgemeinschaft through award of a research grant (L. F.).

The sodium amide used in this reaction could effect both the elimination to give *(2)* and the subsequent isomerization to *(4)*[6].

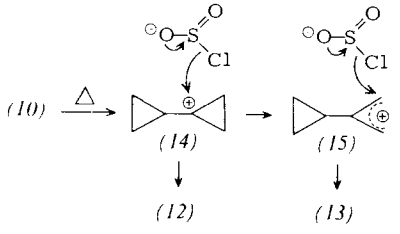
Starting from cyclopropyl methyl ketone *(5)*, we have made 1-chlorobicyclopropyl *(12)*[8] accessible by two independent routes:

1. By geminal dihalogenation to give (1,1-dichloroethyl)cyclopropane *(7)*[10], elimination to give (1-chlorovinyl)cyclopropane *(9)*[11], addition of dibromocarbene, with phenyl(tribromomethyl)mercury as carbene precursor[12] to give 2,2-dibromo-1-chlorobicyclopropyl *(11)*, and selective reduction with tri-*n*-butylhydridotin[13] to give *(12)*; and

2. by reaction of the sodium enolate of *(5)* with trimethylsilyl chloride to give [1-(trimethylsilyloxy)vinyl]cyclopropane *(6)*[14], cyclopropanation by a modified Simmons-Smith reaction[15] to give 1-(trimethylsilyloxy)bicyclopropyl *(8)*, conversion into the chlorosulfite *(10)* (not isolable but detectable spectroscopically), and pyrolysis to give *(12)*. The 2-cyclopropylallyl chloride *(13)* contaminating *(12)* can easily be removed by addition of bromine.

The reaction sequence *(8)* → *(10)* → *(12)* is, to our knowledge, the first example of replacement of a trimethylsilyloxy group by chlorine.

The formation of a preponderant amount of *(12)* rather than of *(13)* in the pyrolysis of *(10)* is further evidence of the relative stability of the 1-cyclopropylcyclopropyl cation *(14)*. This ion undergoes only slight ring opening to 2-cyclopropylallyl cation *(15)*[16].



The subsequent elimination of hydrogen chloride from 1-chlorobicyclopropyl *(12)* can be effected without any side reaction by using sodium amide in liquid ammonia and leads to bicyclopropylidene *(4)* *via* cyclopropylcyclopropene *(2)*. In agreement with this interpretation the product ratio *(4)*/*(2)* increases greatly on prolongation of the reaction time; after 18 h we obtained 15% of *(2)* and 52% of *(4)*. Subsequent distillation afforded 40% of pure bicyclopropylidene *(4)*, b.p. 101 °C, with complete polymerization of *(2)*. It is to be expected that the yield of *(4)* can be further increased[18].

(2) could be unambiguously identified in admixture with *(4)* by means of its characteristic methine-proton signal [$\tau = 4.10$ ppm, $J = 3$ Hz (pentane)]. The spectroscopic data for *(4)*[3], *(7)*[10b], *(9)*[10a] and *(12)*[9] were in accord with those reported in the literature.

All the new compounds gave satisfactory analytical values. Their most important physical and spectroscopic data are collected in Table 1.

We prefer the synthesis by way of *(6)*: it permits *(4)* to be obtained on a preparative scale by use of commercially available reagents.

Table 1. Physical and spectroscopic data for compounds *(6)*, *(8)*, *(11)*, and *(13)*.

Cpd.	B.p. [°C/torr]	IR [a] [cm^{-1}]	^{1}H-NMR [b] τ[ppm]
(6)	145/760	ν_{C-H} 3114, 3092, 3012 2960, 2900 $\nu_{C=C}$ 1648	d 5.98 (1) (J = 1 Hz), d 6.11 (1) (J = 1 Hz), m 8.45—8.90 (1), m 9.35—9.65 (4), s 9.82 (9)
(8)	65/23	ν_{C-H} 3082, 3006, 2956 2896	m 8.50—9.10 (1), m 9.40—9.80 (8), s 9.90 (9)
(11)	52/0.015	ν_{C-H} 3085, 3011	s 8.21 (2), m 8.25—8.70 (1), m 9.05—9.75 (4)
(13)	[c]	ν_{C-H} 3083, 3004, 2950 $\nu_{C=C}$ 1642	q 5.03 (1) (J = 1 Hz), t 5.23 (1) (J = 1 Hz), d 6.01 (2) (J = 1 Hz), m 8.30—8.90 (1), m 9.10—9.50 (4)

[a] Characteristic IR frequencies, measured for pure liquids.
[b] Measured for CCl_4 solutions with TMS as internal standard.
[c] Purified by gas chromatography; *(13)* cannot be separated from *(12)* (b.p. 75 °C/150 torr) by distillation.

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[1] *J. L. Ripoll, J. C. Limasset*, and *J. M. Conia*, Tetrahedron *27*, 2431 (1971), and literature cited therein.

[2] *L. Fitjer* and *J. M. Conia*, Angew. Chem. *85*, 349 (1973); Angew. Chem. internat. Edit. *12*, 334 (1973).

[3] *P. LePerchec* and *J. M. Conia*, Tetrahedron Lett. *1970*, 1587.

[4] *A. J. Schipperijn*, Rec. Trav. Chim. Pays-Bas *90*, 1110 (1971).

[5] *G. L. Closs* and *R. D. Krantz*, J. Org. Chem. *31*, 638 (1966).

[6] Eliminations from three-membered rings with subsequent double bond migration to the *exo*-position are known [7]. The bases used hitherto were almost exclusively alkali-metal alkoxides (sodium hydride-ethanol in ether [7a], potassium isopropoxide [7b, d], and potassium *tert*-butoxide [7c, e—h] in DMSO).

[7] a) *J. A. Carbon, W. B. Martin*, and *L. R. Swett*, J. Amer. Chem. Soc. *80*, 1002 (1958); b) *T. C. Shields, B. A. Shoulders, J. F. Krause, C. L. Osborn*, and *P. D. Gardner*, *ibid. 87*, 3026 (1965); c) *C. L. Osborn, T. C. Shields, B. A. Shoulders, J. F. Krause, H. V. Cortez*, and *P. D. Gardner*, *ibid. 87*, 3158 (1965); d) *T. C. Shields* and *P. D. Gardner*, *ibid. 89*, 5425 (1967); e) *T. C. Shields* and *W. E. Billups*, Chem. Ind. (London) *1967*, 1999; f) *M. Bertrand* and *H. Monti*, C. R. Acad. Sci. Paris *C 264*, 998 (1967); g) *T. C. Shields, W. E. Billups*, and *A. R. Lepley*, J. Amer. Chem. Soc. *90*, 4749 (1968); h) *W. Eymann* and *M. Hanack*, Tetrahedron Lett. *1972*, 4213.

[8] 1-Chlorobicyclopropyl *(12)* was first obtained by *Landgrebe* and *Becker* [9] by photochlorination of bicyclopropyl, but could not be separated from the (1-chloroethyl)cyclopropane also formed.

[9] *J. A. Landgrebe* and *L. W. Becker*, J. Amer. Chem. Soc. *89*, 2505 (1967); *90*, 395 (1968).

[10] a) *M. Hanack* and *T. Bässler*, J. Amer. Chem. Soc. *91*, 2117 (1969); b) *C. E. Hudson* and *N. L. Bauld*, *ibid. 94*, 1158 (1972). An almost quantitative yield of *(7)* is obtained when the free hydrogen chloride in a suspension of phosphorus pentachloride in methylene dichloride is bound by 0.1 equivalent of pyridine before addition of *(5)*.

[11] Short heating of equivalent amounts of *(7)* and quinoline suffices to effect the elimination. Use of potassium hydroxide in triethylene glycol [10a] offers no advantage over this.

[12] *D. Seyferth* and *R. L. Lambert jr.*, J. Organometal. Chem. *16*, 21 (1969); see also *D. Seyferth*, Accounts Chem. Res. *5*, 65 (1972), and literature cited therein.

[13] *D. Seyferth, H. Yamazaki*, and *D. L. Alleston*, J. Org. Chem. *28*, 703 (1963).

[14] The methods used for preparation of trimethylsilyl enol ethers [for a review see: *H. O. House, L. J. Czuba, M. Gall*, and *H. D. Olmstead*, J. Org. Chem. *34*, 2324 (1969)] essentially differ only as concerns the type of base used for formation of the enolate. Sodium amide has the advantage over the bases used previously that ammonia and sodium chloride are the only products accompanying the desired enol ether. Filtration and removal of the solvent (ether) suffice for isolation of the crude enol ether.

[15] *J. M. Denis, C. Girard*, and *J. M. Conia*, Synthesis *1972*, 549.

[16] Cf. also the results of solvolyses with 1-chlorobicyclopropyl [9], 1-(tosyloxy)bicyclopropyl [17a], 2,2-dideuterio-1-(tosyloxy)bicyclopropyl [17b], and (tosyloxymethyl)spiropentane [17c].

[17] a) *B. A. Howell* and *J. G. Jewett*, J. Amer. Chem. Soc. *93*, 798 (1971); b) *R. A. Martin* and *J. A. Landgrebe*, J. Org. Chem. *37*, 1996 (1972); c) *J. J. Gajewski* and *J. P. Oberdier*, J. Amer. Chem. Soc. *94*, 6053 (1972).

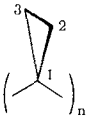
[18] *Note added in proof* (March 15, 1973): A 55% yield of pure *(4)* could be obtained by treatment of *(12)* with potassium *tert*-butoxide in DMSO.

Tricyclopropylidene ([3]-Rotane)[**]

By *Lutz Fitjer* and *Jean-Marie Conia*[*]

Polycyclopropylidenes ([*n*]-rotanes) *(1)*[1] are of particular interest because of the question whether their cyclopropane rings, which are linked to one another in *s-cis* fashion without interruption, could lead to an electron system delocalized over the central ring.

A qualitative assessment on the basis of the "bent-bond" model for cyclopropane[2] shows that this delocalization becomes the more probable the smaller the angle (β) between the planes of two neighboring cyclopropane rings and the greater the p contribution to the cyclopropane hybrid orbitals directed from C-1 to C-2 and from C-1 to C-3.



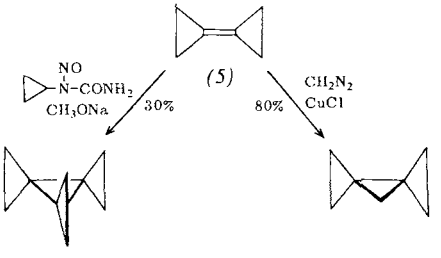
(1), n = 3, 4, 5...

Thus the conditions for a possible delocalization are most favorable for hexacyclopropylidene ([6]-rotane) *(1)*, $n=6$ ($\beta=60°$, hybridization C-1, C-2=C-1, C-3=sp^5) and least favorable for tricyclopropylidene ([3]-rotane) *(1)*, $n=3$ ($\beta=120°$, C-1, C-2=C-1, C-3=sp^3)[3][4].

We report here the synthesis of tricyclopropylidene *(1)*, $n=3$, and show, by spectroscopic comparison with dispiroheptane *(2)*, spiropentane *(3)*, and cyclopropane *(4)* that for *(1)*, $n=3$, a delocalization of the cyclopropane hybrid orbitals over the central ring is to be excluded.

Tricyclopropylidene *(1)*, $n=3$, could be obtained by spiroalkylation of bicyclopropylidene *(5)*[5] with 1-cyclopropyl-1-nitrosourea[6] as source of cyclopropylidene. Spiroalkylations of that type are known[7] but have hitherto been carried out in presence of a large excess of olefin. We, however, used an excess of 1-cyclopropyl-1-nitrosourea and obtained a 30% yield of the desired tricyclopropylidene *(1)*, along with allene.

The compounds *(2)*[8] and *(3)* required for comparison were prepared by CuCl-catalyzed reaction of *(5)* with diazomethane[10] and according to ref. [11], respectively.



(1), n = 3 *(2)*

In spite of the expected high strain energy, pure tricyclopropylidene *(1)*, $n=3$ (m. p. 29—31 °C), is thermally extremely stable. Heating for an hour at 300 °C does not lower its melting point, and the substance decomposes only at about 350 °C. Its structure is proved by spectroscopic data (see Table 1).

Table 1. Spectroscopic data for the compounds *(4)*, *(3)*, *(2)*, and *(1)*, $n=3$.

Cpd.	IR [a] [cm^{-1}] ν_{C-H}	^{1}H-NMR [b] τ [ppm] $(CH_2)_a$	$(CH_2)_b$	^{13}C-NMR [c] δ (ppm) $(^{13}C)_a$	$(^{13}C)_b$	$(^{13}C)_c$	$J^{13}C-H$ [d] [Hz]	UV [e] λ [nm] (ε)
(4)	3081 [13] 3013	s 9.87 [14] 9.78 [15]		196.3 [16] 195.7 [17]			161.8 [14] 162 ± 2 [16]	
(3)	3080 3012	s 9.24	s 9.24	186.8	186.8	180.9	159.8 [14] 162 ± 3	232.0 (42)
(2)	3062 2980	s 8.85	m 9.30 [f]	179.0	187.4	178.4	160 ± 2 [g]	201.5 (15) 209.5 (16) 262 (3)
(1), $n=3$	3060 2982		s 9.34		188.0	174.5	162 ± 2	205.0 (30) sh 212.5 (34) 262 (2)

[a] Measured for CCl_4 solutions, except for *(4)* (capillary).
[b] Measured for CCl_4 solutions with TMS as internal standard.
[c] Proton decoupled spectra; measured for $CDCl_3$ solutions with TMS as internal standard. The chemical shifts obtained were converted to CS_2 as standard by using the relation $\delta(CS_2)=\delta(TMS)+192.8$ [18].
[d] Taken from non-decoupled ^{13}C-NMR spectra; the relatively large range of error is ascribed to the complexity of the spectra caused by $^{13}C-C-H$ long-range couplings.
[e] Measured for cyclohexane solutions; sh = shoulder.
[f] Center of an AA'BB' line system with $\nu_A - \nu_B \approx 0.20$ ppm.
[g] $(J^{13}C-H)_a$; $(J^{13}C-H)_b$ could not be determined because the number of accumulations was too small.

Because of the low intensity of the molecular ion (< 1%) we have determined the exact mass of $M-1$, which is characteristic for many cyclopropane derivatives[12]. Calculated (119.086) and experimental values (119.086 ± 0.002) showed the expected agreement.

Whether tricyclopropylidene *(1)*, $n=3$, possesses a delocalized electron system can be decided by comparison of

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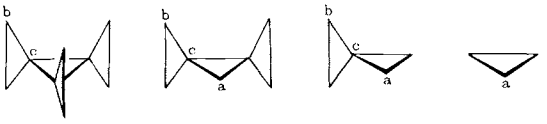
[**] Etude des Rotanes, Part V. – Part IV: [1e]. This work was supported by the Deutsche Forschungsgemeinschaft by award of a research grant (L. F.). We thank Jeolco Ltd., Grove Park-Edgware Road, London, N.W. 9, for determining the ^{13}C-NMR spectra.

the spectroscopic data for *(4)*, *(3)*, *(2)*, and *(1)*, $n=3$ (see Table 1).



(1), n = 3 *(2)* *(3)* *(4)*

Whilst the approximate agreement of the C—H stretching frequencies and ^{13}C—H coupling constants is not surprising and is no argument for or against the existence of conjugative interaction of the cyclopropane rings in *(1)*, $n=3$, the almost identical UV spectra of *(1)*, $n=3$, and *(2)* can be regarded as evidence that *(1)*, $n=3$, represents no exception in the series *(4)*, *(3)*, *(2)*, *(1)*, $n=3$.

This is shown still more clearly by comparison of the ^1H- and ^{13}C-NMR data. As would be expected if only inductive effects were operative, the ^1H- and ^{13}C-resonance signals are shifted by almost constant amounts along the series *(4)*, *(3)*, *(2)*, *(1)*, $n=3$: $\tau(CH_2)_a$ and $\delta(^{13}C)_a$ consecutively by about 0.5 and 9 ppm, respectively, downfield, and $\tau(CH_2)_b$ and $\delta(^{13}C)_b$ consecutively by about 0.05 and 0.6 ppm, respectively, upfield[19]. Only the ^{13}C-resonance signals of the quaternary carbon atoms that would be intimately concerned in delocalization of the C-1, C-2 and C-1, C-3 hybrid orbitals deviate slightly from the additivity observed elsewhere for the shifts; thus the difference $[\Delta\delta(^{13}C)_c]$ found on passing from *(3)* to *(2)* is 2.5 ppm but increases to 3.9 ppm on passing to *(1)*, $n=3$; yet this deviation is too small to suggest delocalization of the cyclopropane hybrid orbitals in *(1)*, $n=3$.

We therefore expect that the strain energy of *(1)*, $n=3$, will not fall much below the value 135.1 kcal/mol calculated from the strain energies of cyclopropane (27.15 kcal/mol[20]) and spiropentane (63.13 kcal/mol)[20, 21].

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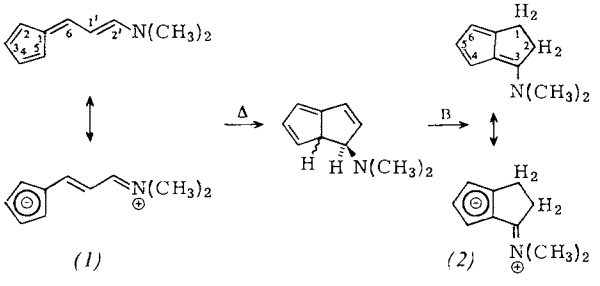
A Simple Synthesis of 1,5-Dihydropentalenes[**]

By *Reinhard Kaiser* and *Klaus Hafner*[*]

Dedicated to Professor B. Eistert on the occasion of his 70th birthday

Dihydropentalenes are important as precursors for a synthesis of pentalene and its derivatives[1]. We recently reported a simple synthesis of 1,2-dihydropentalenes *(2)* by thermolysis of 6-(2'-dimethylaminovinyl)fulvenes *(1)* in the presence of bases[2]. The reaction extends the general principle previously reported by us for the preparation of bi- and poly-cyclic conjugated π-electron systems[3].



(1) *(2)*

When applying this ring-closure reaction to derivatives of *(1)* carrying alkyl or aryl substituents in the side chain we observed that the cyclization and subsequent reactions were strongly dependent on the nature, number, and position of the substituents. Whereas fulvenes of type *(1)* with 6-alkyl or 6-aryl substituents afforded 1-alkyl- or 1-aryl-1,2-dihydro-3-dimethylaminopentalenes[4], the expected 1-alkyl- or 1-aryl-1-dimethylamino- or 1-ethoxy-1,2-dihydropentalenes *(4)* were not formed from terminally alkylated or arylated 6-(2'-dimethylamino- or -ethoxy-vinyl)fulvenes *(3)*[5] in boiling piperidine; the only products isolated were 1-alkyl- and 1-aryl-1,2-dihydro-3-piperidinopentalenes *(6)* which are resonance-stabilized and have lower energy than *(4)*.

These products *(6)* may have been formed in a thermodynamically controlled reaction by nucleophilic attack of the piperidine on the electrophilic center[6] of an initially

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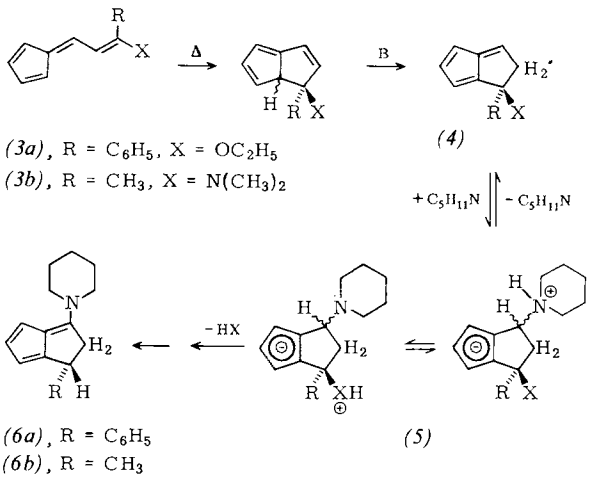
formed intermediate *(4)* and subsequent loss of dimethylamine or ethanol from *(5)*.



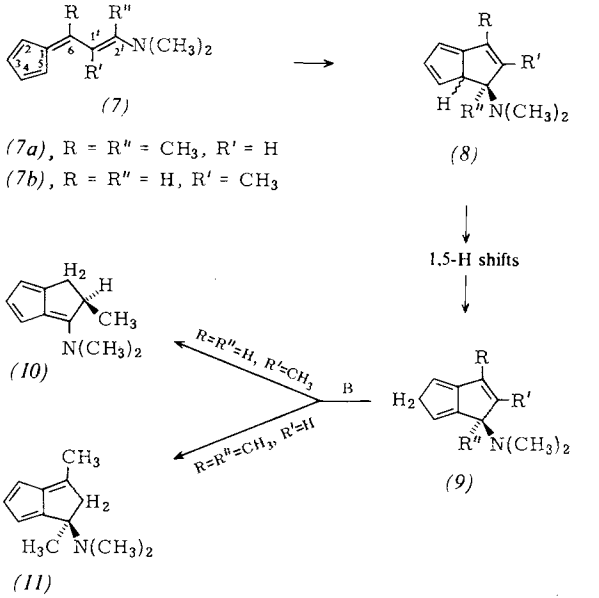
(3a), R = C_6H_5, X = OC_2H_5
(3b), R = CH_3, X = $N(CH_3)_2$

(4)

(6a), R = C_6H_5
(6b), R = CH_3

(5)

On the other hand, 6-(2'-dimethylaminovinyl)fulvenes *(7)*[5] alkylated at position 1' or dialkylated at positions 6 and 2' cyclize even below 20 °C and in the absence of a base. However, no derivatives of 1,2-dihydropentalene are formed, as by the ring closure of *(1)* or *(3)*, but instead the reaction yields the thermally rather unstable 1,5-dihydropentalenes *(9)*[7] which can be isomerized by bases, *e.g.* by piperidine, to the thermodynamically more stable fulvenoid 1,2-dihydropentalenes *(10)* or *(11)*. In



(7)

(7a), R = R'' = CH_3, R' = H
(7b), R = R'' = H, R' = CH_3

(8)

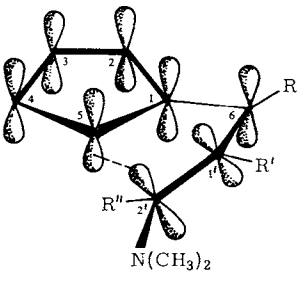
1,5-H shifts

(10)

(9)

(11)

the formation of *(9)* an electrocyclic reaction of *(7)*, giving *(8)*, is probably followed by a double 1,5-H shift characteristic for cyclopentadienes[8]. Consideration of models and UV spectra of *(7)* show that in *(7a)* there is steric hindrance between the substituents in positions 6 and 2' and in *(7b)* between R' on C-1' and the H atom at position 2 or 5; this would be relieved by rotation of the enamine portion around the C(6)—C(1') bond so as to move it out of the plane of the molecule. In the sterically most favored case the p_z-orbitals of C-6 and C-1' form an angle of 60 to 90°. In this process the p_z-orbitals of C-2' and C-5 come so close together that an electrocyclic reaction occurs even below 20 °C, presumably by a conrotatory 8 π-electron process[9]. These conditions favoring cyclization do not arise with *(1)* and *(3)*, for which the transoid conformation of the exocyclic group is favored instead, hence their cyclization requires a higher activation energy. However, under the conditions necessary for this cyclization neither the cyclization products *(8)* (R = R' = H, R'' = H, alkyl, or aryl) nor the 1,5-dihydropentalene derivatives *(9)* (R = R' = H, R'' = H, alkyl, or aryl) expected as a result of 1,5-H shifts are stable; in the thermal cyclization in the presence of bases they are rapidly converted into the more inert, tautomeric, resonance-stabilized, fulvenoid 1,2-dihydropentalenes *(2)* or *(6)*.



Cpd. M.p. [°C] Yield	UV in *n*-hexane λ_{max} [nm] (log ε)	NMR (τ) [c]
(6a) 107–108 75%	315 (4.44) 323 (4.45)	5.54 (m, H-1); 6.30 (qd, H-2, $J_{2,2} \approx 17$ Hz, $J_{1,2} \approx 7.5$ Hz); 7.04 (qd, H-2, $J_{1,2} \approx 2.7$ Hz); 3.71 (qd, H-4, $J_{4,5} \approx 4.5$ Hz, $J_{4,6} \approx 1.2$ Hz); 3.24 (qd, H-5, $J_{5,6} \approx 2.7$ Hz); 4.11 (m, H-6); 2.69 (m, C_6H_5-1); 6.35 (m, $N(CH_2)_2$-3); 8.29 (m, $(CH_2)_3$) [a]
(6b) 82–84 36%	315 (4.46) 321 (4.47)	7.69–6.07 (m, H-1, 2H-2, $N(CH_2)_2$-3); 3.88 (qd, H-4, $J_{4,5} \approx 4.5$ Hz, $J_{4,6} \approx 1$ Hz); 3.36 (qd, H-5, $J_{5,6} \approx 2.5$ Hz); 4.14 (m, H-6); 8.72 (d, CH_3-1, $J \approx 6.6$ Hz); 8.31 (m, $(CH_2)_3$) [a]
(9a) — 75%	214 220 227 260	4.32 (q, H-2, $J \approx 1.5$ Hz); 4.04–4.19 (m, H-4, H-6); 6.68 (m, 2H-5); 8.68 (s, CH_3-1); 7.88 (s, $N(CH_3)_2$-1); 8.09 (d, CH_3-3, $J \approx 1.5$ Hz) [b]
(9b) — 79%	215 221 228 260	5.90 (m, H-1); 4.31 (m, H-3); 3.93 (q, H-4, $J_{4,5} \approx 1.5$ Hz); 6.61 (m, 2 H-5); 3.76 (q, H-6, $J_{5,6} \approx 1.5$ Hz); 8.04 (m, CH_3-2); 7.78 (s, $N(CH_3)_2$-1) [a]
(10) 74–75 60%	312 (4.39) 317 (4.39)	6.41–7.04 (m, H-1, H-2); 7.35–7.71 (m, H-1); 3.84 (qd, H-4, $J_{4,5} \approx 4.5$ Hz, $J_{4,6} \approx 0.8$ Hz); 3.33 (qd, H-5, $J_{5,6} \approx 2.3$ Hz); 4.01–4.20 (m, H-6); 8.65 (d, CH_3-2, $J \approx 7$ Hz); 6.77 (s, $N(CH_3)_2$-3) [a]
(11) — 33%	264 (4.14) 270 (4.12) 377 (2.84)	7.31 (d, H-2, $J_{2,2} \approx 20$ Hz); 6.80 (d, H-2); 3.90 (qd, H-4, $J_{4,5} \approx 5$ Hz, $J_{4,6} \approx 0.6$ Hz); 3.19–3.39 (m, H-5); 4.05 (m, H-6); 8.57 (s, CH_3-1); 7.80 (s, $N(CH_3)_2$-1); 7.88 (t, CH_3-3, $J \approx 1.5$ Hz) [a]

[a] In $CDCl_3$; [b] In CCl_4; [c] TMS as internal standard.

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[4] Cf. [2]; it has not yet been possible to decide experimentally whether in the cyclization in boiling piperidine we are dealing with an electrocyclic reaction or with an intramolecular electrophilic substitution of the five-membered ring after attack by the base at position 6 of the fulvenoid system.

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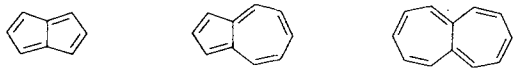
Concerning Pentalene, 2-Methylpentalene, and 1,3-Dimethylpentalene[**]

By *Klaus Hafner, Reinhard Dönges, Ernst Goedecke*, and *Reinhard Kaiser*[*]

In the series of non-alternant bicyclic hydrocarbons, pentalene *(1)* has, unlike azulene *(2)*[1] and heptalene *(3)*[2],



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

withstood attempts at synthesis that have extended over decades[3]. Each of the three compounds contains a peripheral π-electron system perturbed by a central σ-bond; in the case of azulene *(2)*, isomeric with naphthalene and having 10 π-electrons, the system has "aromatic" character, whereas heptalene *(3)* with 12 π-electrons behaves as a cyclopolyolefin. According to the Hückel rule, pentalene, with 8 π-electrons, should not have "aromatic" properties, but quantum-chemical calculations have given contradictory results[4]. Since it is not permissible to draw conclusions about the parent compound from the few known benzo-annelated or highly substituted pentalene derivatives, it is of interest to test the theoretical predictions by synthesis of *(1)* or its simple alkyl derivatives.

Starting from 1,2- and 1,5-dihydropentalene derivatives, for which we have described a simple method of preparation[5-7], we have now been able to detect pentalene *(1)*,

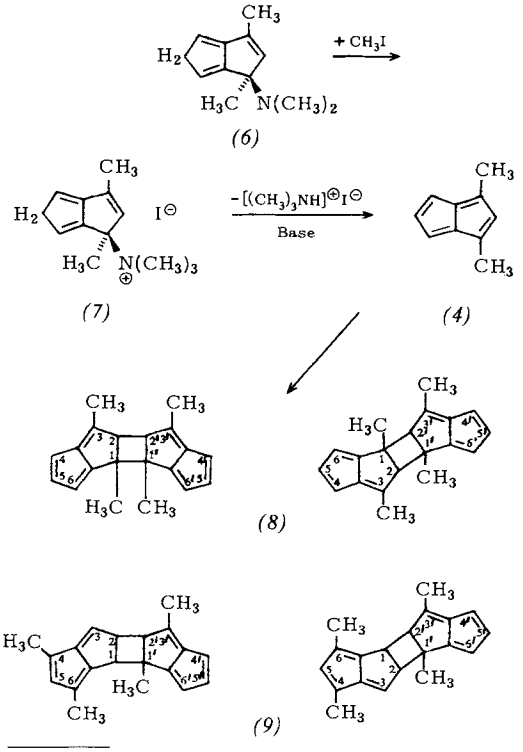


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Table 1. Physical properties of the products *(8)*, *(9)*, *(12)*, and *(14)*.

Cpd.	Yield (%)	M.p. [°C]	UV λ_{max} (nm) (log ε) in *n*-hexane	NMR (τ), *J* (Hz) in CCl_4 [a]
(8a)	32	110–112	267 (4.38) 379 (3.14)	8.43 (CH_3-1/s), 6.91 (H-2/m), 8.00 (CH_3-3/s), 4.16 (H-4/dd), 3.45 (H-5/dd), 4.31 (H-6/m), $J_{4,5}=5.5$, $J_{4,6}=0.5$, $J_{5,6}=2$
(8b)	1.6	80 (dec.)	261, 389	8.65 (CH_3-1/s), 6.53 (H-2/m), 7.95 (CH_3-3/s), 4.26 (H-4/dd), 3.50 (H-5/m), 4.59 (H-6/m), $J_{4,5}=5.5$, $J_{4,6}=0.5$, $J_{5,6}=2$
(8c)	4	180 (dec.)	259 (4.31) 267 (4.38) 284 (4.08) 404 (3.23)	9.03 (CH_3-1/s), 7.30 (H-2/m), 7.81 (CH_3-3/s), 3.98 (H-4/dd), 3.30 (H-5/dd), 4.20 (H-6/m), $J_{4,5}=5$, $J_{4,6}=0.5$, $J_{5,6}=2$
(9a)	4.5	150 (dec.)	256 (4.22) 262 (4.24) 279 (4.05) 408 (3.21)	7.17 (m), 6.61 (m), 6.92 (m) (H-1, H-2, H-2'), 9.05 (CH_3-1'/s), 3.58 (H-3/d), 7.83 (CH_3-3'/s), 7.99 (CH_3-4/d), 4.00 (H-4'/dd), 3.80 (H-5/m), 3.32 (H-5'/dd), 8.10 (CH_3-6/s), 4.25 (H-6'/m), $J_{2,3}=3$, $J_{4,5}=0.5$, $J_{4',5'}=5$, $J_{4',6'}=0.5$, $J_{5',6'}=2$
(9b)	6			6.80 (m), 6.67 (m), 6.50 (m) (H-1, H-2, H-2'), 8.52 (CH_3-1'/s), 3.95–4.00 (H-3, H-5/m), 7.99 (CH_3-3'/s), 8.13 (CH_3-4/d), 4.16 (H-4'/dd), 3.48 (H-5'/dd), 8.23 (CH_3-6/s), 4.49 (H-6'/d), $J_{4',5'}=5$, $J_{4',6'}=1$, $J_{5',6'}=2$
(12a)	22	103–104 (dec.)	254 (4.16) 387 (3.02)	6.25–6.43 (H-1/dm), 5.69–5.99 (H-2/dm), 3.71 (H-3/m), 4.11 (H-4/dd), 3.33 (H-5/dd), 4.35 (H-6/m), $J_{4,5}=5$, $J_{4,6}=0.8$, $J_{5,6}=1.8$
(12b)	10	84 (dec.)	254 (4.21) 259 (4.22) 275 (4.07) 400 (3.17)	7.05 (H-1/dm), 6.39 (H-2/dm), 3.26 (H-3/m), 3.92 (H-4/dd), 3.23 (H-5/dd), 4.01 (H-6/m), $J_{4,5}=5.1$, $J_{4,6}=0.7$, $J_{5,6}=1.8$
(14a)	26	106–107 (dec.)	257 (4.20) 272 (4.11) 382 (2.90)	6.35–6.53 (H-1/m), 5.84–6.04 (H-2/m), 3.97 (H-3/m), 4.43 (H-4/m), 8.00 (CH_3-5/s), 4.52 (H-6/m)
(14b)	12	140 (dec.)	258 (4.25) 263 (4.28) 276 (4.15) 392 (3.06)	7.00–7.13 (H-1/m), 6.38–6.56 (H-2/m), 3.48 (H-3/m), 4.22 (H-4/m), 7.88 (CH_3-5/s), 4.15 (H-6/m)

[a] TMS as internal standard.

1,3-dimethylpentalene *(4)*, and 2-methylpentalene *(5)* directly or by formation of their dimerization products.

Treating 1-(dimethylamino)-1,5-dihydro-1,3-dimethylpentalene *(6)*[6, 7] with methyl iodide in ether at −25 °C affords the methiodide *(7)* (yield 92%, dec. >75 °C). At 25 °C *(7)* undergoes 1,4-elimination in ethanol in the presence of a base yielding 1,3-dimethylpentalene *(4)*[8], whose existence as a short-lived intermediate is strongly suggested by isolation of dimerization products of structures *(8)* and *(9)* that are formed rapidly under the experimental conditions[6]. For each of *(8)* and *(9)* four configurations around the cyclobutane ring are possible and, of these, three stereoisomers were isolated for *(8)* [*(8a)*, *(8b)*, and *(8c)*] and two for *(9)* [*(9a)* and *(9b)*] (see Table 1).

On photolysis[9] of the dimer *(8a)* in a methylcyclohexane/2-methylbutane matrix (1:4) at −196 °C by means of monochromatic light of wavelength 254 nm, the extinctions of the maxima of *(8a)* were observed to decrease whilst a new maximum was formed at 336 nm (Figure 1).

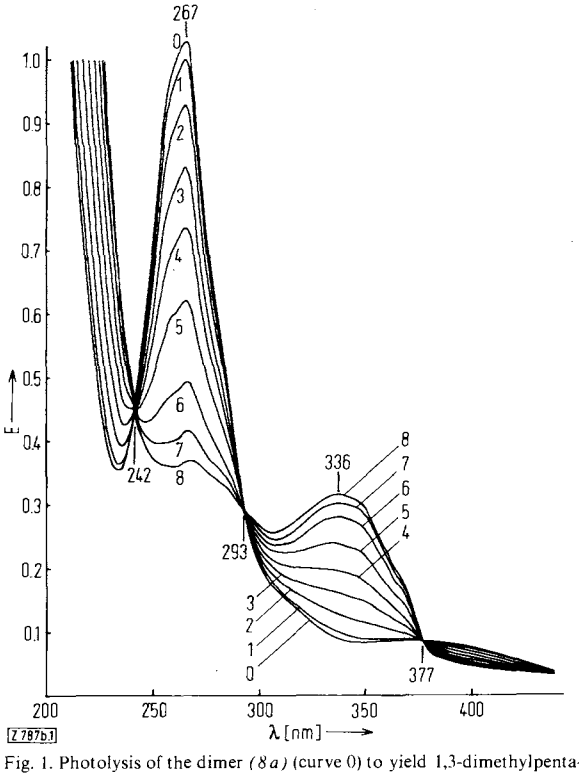
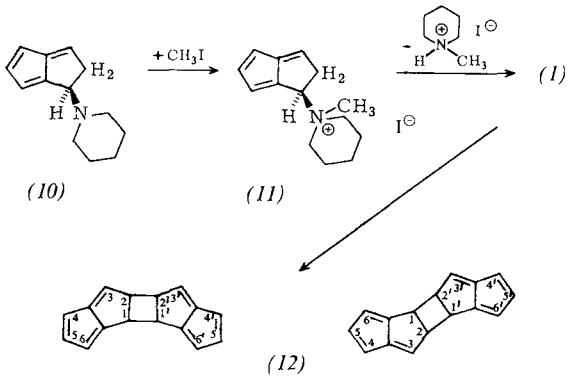


Fig. 1. Photolysis of the dimer *(8a)* (curve 0) to yield 1,3-dimethylpentalene *(4)* (curve 8). The absorption curves 1 to 8 were measured after 15 min, 1, 2, 4, 6, 10, and 25 h, respectively.

When the matrix was warmed to 20 °C this photochemical rearrangement, characterized by three isosbestic points, was seen to be thermally largely reversible. The absorptions of the product from *(8a)* are in excellent agreement with the values determined quantum-chemically for absorption by *(1)*[4d] and accord with the data of *de Mayo et al.* for 1-methylpentalene[10]. Thus the photochemical conversion of the dimeric 1,3-dimethylpentalene *(8a)* may be a [2+2]-cycloreversion with formation of 1,3-dimethylpentalene *(4)*.

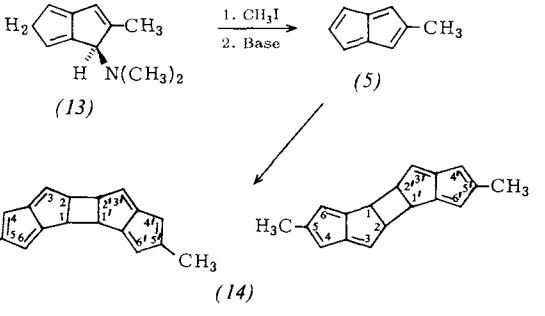
For preparation of pentalene *(1)* 1,2-dihydro-1-piperidinopentalene *(10)*[11] [a yellow thermolabile oil; λ_{max} (log ε) = 257 (3.98), 260 (3.97), 264 (3.94), 275 (3.65), 340 nm (3.08) in *n*-hexane; NMR spectrum (in CCl_4): multiplets



centered at τ = 3.28 (H-5), 3.44 (H-3), 4.00 (H-4, H-6), 6.01 (H-1), 6.97 (2H-2), 7.62 and 8.57 ($C_5H_{10}N$)] was converted into the methiodide *(11)* (yield 47%, dec. >100 °C) by methyl iodide in ether at −25 °C. In ethanol in the presence of a base this underwent Hofmann degradation at a temperature as low as 20 °C, after which two pentalene dimers of structures *(12)* were isolated in 22 and 10% yield, respectively; they are stereoisomers of *(12)* with respect to the cyclobutane ring fusions[11, 12] (see Table 1).

The results of photolysis of the dimers *(12a)* and *(12b)* under the same conditions as for the dimer *(8a)* indicate a fission of the dimers here too.

Analogously to the formation of the dimers of 1,3-dimethylpentalene *(4)*, two dimers *(14)* (or their stereoisomers with respect to the cyclobutane ring fusions) (Table 1) of the presumed intermediate 2-methylpentalene *(5)* were isolated from 1-(dimethylamino)-1,5-dihydro-2-methylpentalene *(13)*[7].



Experiments are at present being carried out in an attempt to identify the pentalene *(1)* and its derivatives *(4)* and *(5)*.

German version: Angew. Chem. 85, 362 (1973)

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[8] On thermolysis 1-(dimethylamino)-1,2-dihydro-1,3-dimethylpentalene [isomeric with *(6)*] [7] or its methiodide or *N*-oxide affords 1,2-dihydro-3-methyl-1-methylenepentalene as a red oil, sensitive to oxygen

[λ_{max} (log ε) = 214 (4.16), 221.5 (4.00), 237.5 (4.06), 244.5 (4.18), 253 (4.18), 263 (3.95), 273 (4.00), 285 (3.91), 406 nm (3.22) in *n*-hexane; NMR spectrum ($CDCl_3$): τ = 4.87, 4.43 (m, 2H-9), 6.33 (m, 2H-2), 7.70 (m, CH_3-3), 3.45—3.62 (m, H-4, H-6), 2.82—3.03 (m, H-5)].

[9] We thank Prof. *G. Quinkert*, Dipl.-Chem. *K. Kaiser*, and Dipl.-Chem. *K. Schmieder* (Universität Frankfurt/Main) for advice and help in carrying out the photolyses.

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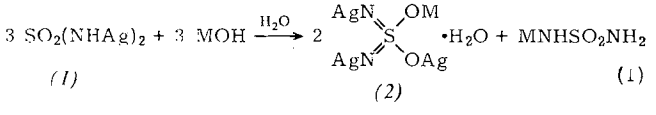
[11] Reduction of 1,2-dihydro-1,3-dipiperidinopentalene (pale yellow crystals, m. p. 99 °C) by lithium tetrahydridoaluminate gave *(10)* in 65% yield. The starting material can be prepared by condensation of sodium cyclopentadienide with 3-(dimethylamino)-3-ethoxy-*N*,*N*-dimethylpropen-2-aldimonium tetrafluoroborate, which gives 6-(2'-ethoxy-2'-dimethylaminovinyl)fulvene (red needles, m. p. 54 °C, yield 70%), with final cyclization in boiling piperidine (yield 46%).

[12] Primary formation of pentalene *(1)* before formation of the dimers is also indicated by isolation of the dimer *(12a)* on dehydrogenation of 1,2-dihydropentalene [5] at 480 °C in presence of a Pd/C catalyst *in vacuo*.

Dinitridodioxosulfate(VI), $SN_2O_2^{4-}$: A New Derivative of the Sulfate Ion

By *Edgar Nachbaur* and *Alois Popitsch*[*]

Reaction of sulfuric diamide with silver nitrate in aqueous solution followed by neutralization with ammonia gives the sparingly soluble, white *N*,*N'*-diargentosulfuric diamide *(1)*[1]. This is converted by alkali hydroxide or ammonia solution in excess into yellow products with a higher silver content. For example, *(1)* and 2 N NaOH at room temperature give monosodium trisilver dinitridodioxosulfate(VI) monohydrate *(2)* (M = Na) and *N*-sodiosulfuric diamide; the former is also only sparingly soluble, but the latter remains in solution.

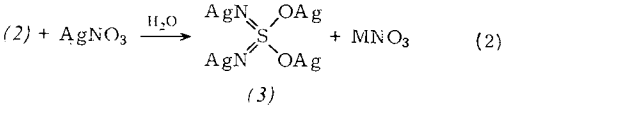


(1) *(2)* (1)

M = Li, Na, K, NH_4

Reaction of *(2)* with hydrogen sulfide in anhydrous methanol affords a mixture of sulfuric diamide and sodiosulfuric diamide, as can be demonstrated spectroscopically, and this confirms the stoichiometry of eq. *(1)*.

On digestion of *(2)* with an excess of warm aqueous silver nitrate solution one obtains the insoluble dark red tetrasilver dinitridodioxosulfate(VI) *(3)*:



(2) *(3)* (2)

If *(3)* is treated in the same way with H_2S, then sulfuric diamide is quantitatively regenerated. The composition of *(2)* and *(3)* is proved by elemental analysis. The IR spectra accord with the tetrahedral structure (C_{2v}) assumed for the $SN_2O_2^{4-}$ ion: IR spectrum of *(3)* (KBr; cm^{-1}): 1080 ν_{as}(S=N) vs; 935 ν_s(S=N) vs; 890 ν_{as}(S—O) vs; 785 ν_s(S—O) vs; 670 s, 620 s, 580 s, 375 s.

The silver salts *(2)* and *(3)* are insoluble in all the usual solvents and are thermally unstable, particularly compound *(3)* which in the dry state decomposes explosively on mechanical shock (rubbing, impact) with deposition of metallic Ag.

Experimental:

Concentrated NH_3 solution (100 ml) is added to $SO_2(NH_2)_2$ (4.8 g, 0.05 mol) and $AgNO_3$ (17 g, 0.1 mol) under red light, and the mixture is concentrated to 10 ml in a rotary evaporator. The white crystalline precipitate *(1)* is filtered off and washed with water; when heated with 5% NH_3 solution in excess it changes almost quantitatively to the pale yellow trisilver salt *(2)*.

The salt *(2)* (1 g) is digested with $AgNO_3$ (5 g) in H_2O (100 ml) in a beaker protected from light and heated on a water-bath. Dark red tetrasilver salt *(3)* is then formed and can be washed with water, alcohol, and ether and stored under an inert solvent. Yield almost 100%.

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$^{13}C^{13}C$ Coupling Constants of 1,3-Butadiene[**]

By *Georg Becher*, *Wolfgang Lüttke*, and *Gerd Schrumpf*[*]

The bonding in 1,3-butadiene is of fundamental importance in the question of the extent of delocalization of the π-electrons of unsaturated molecules. Increased interest attaches to $^{13}C^{13}C$ coupling constants for the study of CC bonding[1]. There exists a direct relation[2], which also has a theoretical foundation[3], between the extent of this coupling and the properties of the C atoms participating in the bonding. Thus, we have determined the $^{13}C^{13}C$ coupling constants of 1,3-butadiene[4]. Since it is not possible, even with the techniques available today, to measure these constants precisely for compounds with their natural ^{13}C content, we have analyzed the spectra of several ^{13}C-labeled butadiene molecules. Butadienes were therefore prepared containing one or two ^{13}C atoms enriched to *ca.* 90%.

The coupling constant between non-equivalent ^{13}C atoms can be determined on introduction of only one ^{13}C atom by measuring its coupling with the other ^{13}C atoms left in their natural abundance. The coupling constants are obtained from such ^{13}C-NMR spectra by simultaneous decoupling of all the protons.

It becomes necessary to introduce two ^{13}C atoms when the coupling constant between chemically equivalent ^{13}C nuclei is to be measured. The coupling constant can be determined from the spectrum only if the two ^{13}C nuclei couple with other nuclei, *e.g.* with protons. For such spin systems all the coupling constants can be found from both the ^{13}C- and the ^{1}H-NMR spectrum[5].

To avoid too complicated spectra, as few protons as possible were left in the ^{13}C-labeled molecule; the unnecessary hydrogen atoms were replaced by deuterium, and the spectra were observed under D-decoupling conditions.

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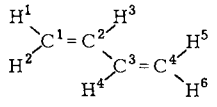
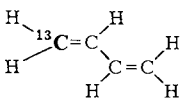


(1)



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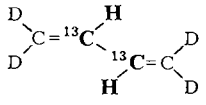

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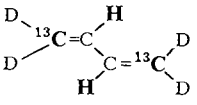
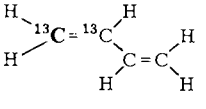


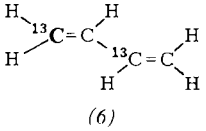
(4)

With these points in mind we have synthesized the following compounds: [1-^{13}C]-1,3-butadiene *(2)*, [1,1,4,4-$^{2}H_4$][2,3-$^{13}C_2$]-1,3-butadiene *(3)* and [1,1,4,4-$^{2}H_4$][1,4-$^{13}C_2$]-1,3-butadiene *(4)*. Formula *(1)* shows the numbering. The spectra of these compounds afforded all the CC and most of the CH coupling constants.

Analysis of the ^{1}H-NMR spectrum of *(2)* has already been reported[6]. The ^{13}C-NMR spectrum of *(2)* was obtained by the Fourier technique with proton decoupling. Because of the natural abundance of ^{13}C, about 1% each of the doubly labeled compounds *(5)* and *(6)* existed alongside *(2)*, and their spectra are superposed on that of *(2)*.



(5)



(6)

From the AX spectrum of *(5)* one obtains $J_{C^1C^2}$ at 68.8 Hz. The two doublets of the AX system of *(6)* could not be resolved. Their half-width yielded only an upper limiting value of 1 Hz for $J_{C^1C^3}$.

We obtained the coupling constants of the AA'XX' spin systems of *(3)* and *(4)* not from the ^{13}C spectra, but from the ^{1}H spectra with decoupling of the deuterons because of the considerably greater accuracy of the latter measurements. Numerical analysis of the spectrum of *(3)* gave $J_{C^2C^3}$ and that of *(4)* led to $J_{C^1C^4}$.

$J_{C^2H^3}=152.74$ and $J_{C^2H^4}=4.07$ Hz, as well as $J_{C^1H^3}=0.01$ and $J_{C^1H^4}=4.42$ Hz, were also obtained. Table 1 lists all the chemical shifts and coupling constants.

The magnitude of the CC coupling constants $^1J_{CC}$ across one bond is primarily determined by the hybridization of the carbon orbitals that form the bond[2]. Thus, the numerical value of $^1J_{CC}$ in the series ethane (sp^3-sp^3), ethylene (sp^2-sp^2), and acetylene (sp-sp) increases from 34.6, by way of 67.6, to 171.5 Hz[7]. The value 68.8 Hz found in this work for $J_{C^1C^2}$ in 1,3-butadiene lies in the double-bond region, as expected.

Table 1. Chemical shifts and coupling constants of the ^{13}C atoms of 1,3-butadiene [a].

	C^1	C^2	C^3	C^4
C^1	−10.40	68.8	<1	9.05
	(0.04)	(0.4)	(0.4)	(0.03)
C^2		10.06	53.70	<1
		(0.04)	(0.05)	(0.4)
C^3			10.06	68.8
			(0.04)	(0.4)
C^4				−10.40
				(0.04)

[a] See *(1)* for the numbering of the atoms. All the coupling constants (non-diagonal elements) are in Hz; the chemical shifts (diagonal elements) are in ppm relative to C_6D_6. Data in parentheses are standard deviations.

We presume that the exact value of $^1J_{CC}$ also depends on the number of carbon-substituents on the double bond. This is indicated by the increase of this coupling from unsubstituted ethylene by way of propene with 70.0 to isobutene with 72.6 Hz[8]: $^1J_{C=C}$ increases by 2–3 Hz per carbon substituent. Styrene with $^1J_{C=C}=70$ Hz fits into this series[2].

The influence of hybridization and an additive effect of carbon-substituents cannot fully explain the exact value of $J_{C^1C^2}$ of butadiene. In comparison with propene, for example, this coupling is shifted to lower values, although both molecules are monosubstituted ethylenes. Therefore it is probable that this decrease in $J_{C^1C^2}$ arises from a decrease in the π-bond order of the double bond in butadiene when compared with that in propene[2]; for even with benzene, where the bond order of each C—C bond is 0.67, one observes a decrease, here indeed of more than 10 Hz ($^1J_{CC}=57.0$ Hz)[9].

The magnitude of $J_{C^2C^3}$ of the formal single bond in butadiene supports this view: $J_{C^2C^3}$ at 53.70 Hz is distinctly lower than in benzene. Thus the π-character of this bond is lower than in benzene; it will hardly exceed a value of *ca.* 0.2. This is in agreement with the electron distribution as determined by theory[10] and with the experimentally observed properties of butadiene[11]. A more precise numerical value for the π-bond order of the two CC bonds in butadiene cannot be determined from our data or from those in the literature: although in all the molecules available for comparison both of the C atoms concerned in the bonding under consideration are sp^2-hybridized, they differ from butadiene in their degree of substitution and in their conformation. In spite of this last limitation we come to the conclusion that the neglect of the π-electron contribution to $^1J_{CC}$, as in a recent publication on CC coupling constants[12], seems to be unjustified. How strongly $^1J_{CC}$ depends on the individual factors discussed above is to be more closely examined by means of the various methylethylenes.

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Kinetic Investigations of Anodic Oxide Layers on Niobium and Tantalum

By *K. E. Heusler*[*]

Non-porous oxide layers of uniform thicknesses between about 50 Å and 0.5 μm can be deposited on niobium or tantalum by anodic oxidation in electrolyte solutions. The glass-like oxides have the composition $M_2O_{5(1-x)}$. The oxygen deficiency creates oxygen vacancies whose concentration may approach several percent of the oxygen sites available.

The concentration of vacancies is increased by dissolution of oxygen from the oxide into the underlying metal and is decreased by reaction of the vacancies with molecular oxygen. Below 400 °C these reactions do not alter the thickness of the layer or its crystallinity.

When studying these reactions, the fact that the anodic oxides on niobium and tantalum are impurity semiconductors[1,2], whose electronic conductivity is a measure of the concentration of oxygen vacancies, was utilized. The electronic conductivity of oxide layers on niobium measured at a constant temperature increases by up to nine powers of ten during heat treatment in vacuum for several hours at temperatures between 100 and 250 °C. This effect is partly due to an increase of the concentration of vacancies. There is also a substantial contribution from the lowering of the activation energy of electronic conductivity with increasing concentration of vacancies. However, the activation energy remains constant in certain ranges of concentration. There the experiments show the concentration of vacancies to rise at a constant rate. The rate-determining step is the transfer of oxygen atoms through the interface from the oxide into the metal[3].

The reaction of oxygen vacancies in niobium oxide with oxygen is also determined by the phase-boundary reaction. Its rate is proportional to the oxygen pressure and to the square of the vacancy concentration. The mechanism suggested is that in a first, rapid step an oxygen molecule occupies a vacancy on the surface and that two normal oxygen ions are formed in a second, slow step by reaction of a second vacancy with the intermediate, involving cleavage of the oxygen-oxygen bond.

The reaction between oxygen vacancies in anodic tantalum oxide and oxygen was investigated with a quartz frequency balance[2]. The frequency of a quartz oscillator decreases linearly with the mass per unit area[4]. The quartz crystals were coated on both sides by anodized tantalum layers. The accuracy of the measurements was about 10^{-9} g $cm^{-2} d^{-1}$. Vacancies were generated by heating the sample *in vacuo*. The kinetics of the increase of mass observed after exposure to oxygen is typical of a reaction whose rate is determined by the phase-boundary reaction at low oxygen pressures and short times, but by diffusion of vacancies toward the surface of the oxide at high oxygen pressures and long times. The rate of the phase-boundary reaction is proportional to the oxygen pressure. The dependence of the rate on the concentration of vacancies also supports the view that the reactions of the oxygen with oxygen vacancies in anodic oxides of tantalum and niobium are described by the same mechanism.

Lecture at Kiel on December 7, 1972 [VB 363 IE]
German version: Angew. Chem. 85, 311 (1973)

[1] *D. Stützle* and *K. E. Heusler*, Z. Phys. Chem., N. F. 65, 201 (1969).
[2] *P. Schulze* and *K. E. Heusler*, unpublished.
[3] *K. E. Heusler* and *P. Schlüter*, Werkst. Korros. 20, 195 (1969); Z. Phys. Chem., N. F. 69, 140 (1970); *P. Schlüter*, Dissertation, Universität Stuttgart 1971.
[4] *G. Sauerbrey*, Z. Phys. 155, 206 (1959).

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Molecular Structure and Biosynthesis of the Fatty Acid Synthetase-Multienzyme Complex of Yeast

By *Eckhart Schweizer*[*]

The fatty acid synthetase complex of the yeast *Saccharomyces cerevisiae* is coded by two unlinked, complex gene loci, *fas*1 and *fas*2[1,2]. Whereas *fas*1 could be localized on chromosome XI of the revised gene map of yeast (formerly chromosome fragment 5), the position of *fas*2 is so far unknown[3].

Genetically and biochemically pleiotropic mutants of both *fas*-gene loci are known[2]. As a rule, they do not synthesize material (CRM) that cross-reacts immunologically with specific fatty acid synthetase antiserum. Synthetase-analogous CRM is, however, formed *in vitro* when cell extracts of suitable CRM-negative, pleiotropic *fas*-mutants are mixed. This *in vitro* complementation indicates that the two *fas*-gene loci are read off independently of one another, and shows further that the native, biologically active conformation of these components are formed only on their association to the total complex. This explains the hitherto unsuccessful attempts to dissociate the complex into enzymatically active partial enzymes.

By feeding radioactive pantothenic acid to various *fas*-mutants it could be shown that in *fas*2 one of the two gene regions responsible for the condensation reaction obviously controls the synthesis of the acyl carrier protein. Mutants of this region contain a pantothein-free fatty acid synthetase complex, which *in vitro* lacks only the condensation reaction.

SDS-polyacrylamide gel electrophoresis permits separation of the fatty acid synthetase complex into two components differing slightly in molecular weight (170000 to 190000). In some mutants one of these two protein bands can be shifted to a different position corresponding to a lower molecular weight. It is thus unlikely that these two bands represent two groups of proteins, each containing different components of the same molecular weight. Rather, the experiments indicate that the two gene loci *fas*1 and *fas*2 each code for a single but polyfunctional peptide chain. Individually, the two chains are obviously enzymatically inactive but on association to the complex undergo a conformational change forming the active sites of the partial enzymes. This association perhaps also yields the active sites of the three acyl transferases for which no individual structural genes have yet been identified.

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Contrary to the structure of bacterial multienzyme complexes, it is probable that multifunctional peptide chains participate in the structure of a series of eukaryotic multienzyme complexes. According to this concept, during the course of evolution an increasing functional structuring of the cell interior would lead not only to formation of multienzyme complexes but also to complexes with multifunctional peptide chains. It is clear that their biosynthesis is favored, both kinetically (by abolition of association) and by regulation (no stoichiometric problem), over the association of the individual partial enzymes.

Lecture at Karlsruhe on January 18, 1973 [VB 364 IE]
German version: Angew. Chem. 85, 365 (1973)

[1] *E. Schweizer, L. Kühn, and H. Castorph*, Hoppe-Seylers Z. Physiol. Chem. *352*, 377 (1971).
[2] *L. Kühn, H. Castorph, and E. Schweizer*, Eur. J. Biochem. *24*, 492 (1972).
[3] *G. Burkl, H. Castorph, and E. Schweizer*, Molec. Gen. Genet., in press

ABSTRACTS

Reviews

Abstracts of selected progress reports and review articles

Enzymes insolubilized on inorganic supports are surveyed by *H. H. Weetall* and *R. A. Messing*. Enzyme derivatives that are insoluble in water have the advantage that they can be used as columns or suspensions and can readily be added to, or removed from, reaction mixtures. Moreover, they can be used repeatedly. Such derivatives are obtained by adsorption or covalent binding of enzymes onto supports. The article describes the available methods, lists the supports used, and considers the properties of some of the resulting preparations. [Insolubilized Enzymes on Inorganic Materials. Chem. Biosurfaces *2*, 563—595 (1972); 101 references]

[Rd 549 IE—G]

Interactions between normal and malignant cells are the subject of a review by *L. Weiss*. It describes the nature of the surface of the cell and the events occurring on cellular contact and subsequently on the surface and in the interior of cells. Interactions with malignant cells are then considered which appear to be responsible for the phenomenon of metastasis, on the one hand, and for tumor resistance, thanks to the destruction of malignant cells by the lymphocytes of the host organism, on the other. [Interactions between Normal and Malignant Cells. Chem. Biosurfaces *2*, 377—447 (1972); 371 references]

[Rd 557 IE—G]

The use of X-ray analysis in studies on amorphous catalysis is surveyed by *P. Ratnasamy* and *A. J. Léonard*. Numerous industrial catalysts (SiO_2,Al_2O_3,SiO_2/Al_2O_3, ultramarines are considered in the present article) possess a large surface area and a high porosity, but are not crystalline and therefore give diffuse X-ray diagrams. However, with the aid of two complementary methods, even such diagrams can provide information about atomic distances and coordination numbers. The methods are described, and the reader is provided with indications regarding experimental techniques. [X-Ray Scattering Techniques in the Study of Amorphous Catalysts. Catal. Rev. *6*, 293—322 (1972); 45 references]

[Rd 561 IE—G]

The role of solvated electrons in electrode processes is dealt with in a review by *B. E. Conway*. Solvated electrons can be formed by photoinjection from the cathode under certain irradiation conditions, by direct injection from the cathode if a sufficiently large potential difference is present at the interface between cathode and solution, and by dissolution of basic metals in solvents such as ammonia and some amines. The article treats experimental proofs of the occurrence of solvated electrons as intermediates in cathodic and photocathodic processes in various media. The electroorganic chemistry of reductions with solvated electrons is considered only in so far as it provides an indication of cathodic production of solvated electrons. [Solvated Electrons in Field and Photo-Assisted Processes at Electrodes. Mod. Aspects Electrochem. *7*, 83—142 (1972); 118 references]

[Rd 563 IE—G]

The IR spectroscopy of nucleic acids is the subject of a review authored by *G. P. Zhizhina* and *E. F. Oleinik*. The article contains IR and Raman data for DNA and RNA as well as their components and deals with the assignment of IR bands to individual bond vibrations. An approach to the theoretical treatment of the normal vibration of the nucleic acid skeleton is described. The authors show how IR provides information about the interactions of heterocyclic bases and about the secondary structures of nucleic acids, as well as their interactions with proteins, metal ions, and a few biologically active substances. [Infrared Spectroscopy of Nucleic Acids. Russ. Chem. Rev. *41*, 258—280 (1972); 218 references]

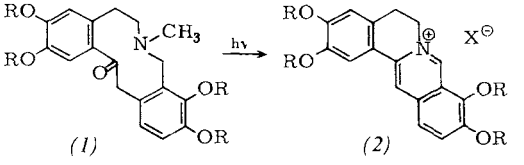
[Rd 589 IE—Q]

The reactivity of cyclic organic phosphorus compounds is reviewed by *R. F. Hudson* and *C. Brown*. The review is based on considerations of the rules of pseudorotation and on the postulates that ring strain decreases a) in the reaction of cyclic phosphoryl or phosphonium compounds with nucleophiles, and b) in the reaction of cyclic P^{III} compounds with nucleophiles to give pentacoordinated

intermediates (with the lone pair of electrons as "phantom ligand"), whereas it increases in the reaction of cyclic P^{III} compounds with electrophiles to give tetracoordinated intermediates. These postulates have been checked experimentally; in almost all the cases studied they have proved to be correct. [Reactivity of Heterocyclic Phosphorus Compounds. Accounts Chem. Res. 5, 204—211 (1972); 57 references]

[Rd 597 IE—L]

The photochemical synthesis of isoquinoline alkaloids is discussed in a review by *T. Kametani* and *K. Fukumoto*. Photolytic electrocyclic reactions are employed *inter alia* for the preparation of aporphine, protoberberine and benzophenanthridine alkaloids. Also of interest is the photochemical transannular reaction in which compounds of the protopine series *(1)* are readily converted into those



(1) *(2)*

of the berberine series *(2)*. The authors also deal with the Pschorr photoreaction (synthesis of alkaloids of the benzyl- and phenylethylisoquinoline series *etc.*) and photolytic cyclodehydrohalogenation (synthesis of aporphine, morphinandienone, proaporphine, and amaryllidaceae alkaloids *etc.*). [Photochemical Synthesis of Isoquinoline Alkaloids, Accounts Chem. Res. 5, 212—219 (1972); 42 references]

[Rd 600 IE—L]

Insolubilized antigens and antibodies are the topic of a review by *H. H. Weetall*. Such antigens and antibodies are also called immunoadsorbents because they serve to isolate, purify, and quantitatively determine the respective antibody or antigene. Furthermore, they are suitable as models for the study of antigene-antibody interactions. The author describes the supports used, the methods of linkage of antigenes or antibodies to these supports, and applications and properties of the resulting products. [Insolubilized Antigens and Antibodies. Chem. Biosurfaces *2*, 597—631 (1972); 130 references]

[Rd 550 IE—G]

The recording of weak IR signals is dealt with by *M. J. D. Low, J. C. McManus*, and *L. Abrams*. It is frequently considered impossible to obtain informative spectra from almost "black" samples. The authors have been disproving this notion for several years with commercially available spectrophotometers and in the present review they show just *what* can be measured under such unfavorable conditions, and *how* one should go about the measurements. [Recording Infrared Spectra at Low Signal Levels. Appl. Spectrosc. Rev. *5*, 171—210 (1972); 33 references]

[Rd 570 IE—G]

Chemisorption complexes and their role in catalytic reactions on transition metals are discussed in a report by *Z. Knor*. The energy of the metallic bond in transition metal crystals lies between 5 and 10 eV, the bond energy of most simple molecules is of the same order of magnitude, and the energy of a chemisorption bond is between 2 and 10 eV. It is therefore difficult to decide whether the interaction between the metal surface and a gas molecule should be described as a perturbation of the crystal by the gas molecule or whether it should be regarded as a surface complex which is perturbed by the crystal. The author favors the second possibility and indicates the consequences for catalysis research. [Chemisorption Complexes and Their Role in Catalytic Reactions on Transition Metals. Advan. Catal. *22*, 51—73 (1972); 85 references]

[Rd 577 IE—G]

Spin-spin coupling constants between geminal and vicinal protons are, as illustrated in a review by *V. F. Bystrov*, sensitive detectors of conformation and structure of molecules. Very slight changes in the structure of the molecule lead to characteristic changes in the coupling constants. The influences of bond length, bond angle, valence, electronic structure and orientation of substituents on the coupling constants is investigated. Unfortunately, present *a priori* calculations do not permit an exact description of the relationships. The author discusses semiempirical approximations that are promising on the basis of general relations from quantum mechanical calculations. [Spin-spin Coupling between Geminal and Vicinal Protons. Russ. Chem. Rev. *41*, 281—304 (1972); 293 references]

[Rd 590 IE—Q]

Patents

Abstracts of selected "Deutsche Offenlegungsschriften" (DOS), *i. e.* provisionally published specifications as filed with the German Patent Office

Polymer masses containing fibrous electrically conducting material can be obtained by the use of glass fibers coated with silver, copper, or nickel as fillers. The compositions may consist of up to 50 wt.% of glass fibers, which have a diameter of 1 to 30 μm and a metal coating 0.025 to 0.25 μm thick. The metal is applied to the glass fibers by immersion in a metal coating bath. Heat-curable resins such as phenolformaldehyde and urea-formaldehyde resins, thermoplastic resins, and rubbers such as polyamides, polyesters, polycarbonates, silicone rubber, natural rubber, and ABS rubber may be used as the polymer. It is possible in this way to avoid the high concentrations of fillers that have been necessary until now in order to obtain appreciable conductivities. [DOS 1720977; Imperial Chemical Industries, Ltd., London]

[PR 39 IE—E]

In a novel production of 3,5-dimethylpyridine, 2-methylene-1,3-propanediol and/or its monoester or diester (acetates) is allowed to react with at least 1/2 equivalent of NH_3, NH_2CH_3, and/or $NH(CH_3)_2$ in the presence of a polar solvent such as H_2O and/or CH_3OH and an acidic catalyst (0.1—10% mineral acid and/or sulfonic acid and/or carboxylic acid) at 200—300 °C and 10—200 atm. The diol can be produced by alcoholysis of the corresponding

diacetate, and can be used as a crude product with a content of 1—30% of monoacetate and/or diacetate. 3,5-Dimethylpyridine is obtained with a purity of 85 to 95%, and can be used in this form *e.g.* for the production of dicarboxylic acids by oxidation. Known processes, on the other hand, lead to mixtures of pyridine derivatives or cause considerable corrosion of the autoclave. [DOS 2045880; Farbenfabriken Bayer AG, Leverkusen]

[PR 49 IE—B]

A new catalyst for the simultaneous production of 1,3-butadiene and methacrolein by treatment of mixtures of *n*-butenes and isobutylene with molecular oxygen can be represented by the following general formula:

$Ni_aCo_bFe_cBi_dX_eMo_fO_gZ_h$

X = phosphorus, arsenic, boron
Z = potassium, rubidium, cesium
$a + b = 1$ to 15, $c = 0.5$ to 7, $d = 0.1$ to 4, $e = 0$ to 4, $f = 12$, $g = 36$ to 98, $h = 0.01$ to 1

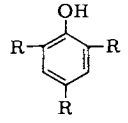
The new catalyst leads to a substantial increase in the yield of 1,3-butadiene and methacrolein in comparison with previously known methods. [DOS 2155109; Nippon Kayaku Co. Ltd., Tokyo]

[PR 50 IE—D]

The racemization of optically active α-amino-ε-caprolactam by microbiological means and a process for the production of L-lysine from D-, L- or DL-α-amino-ε-caprolactam by this racemization method in combination with a microbiological hydrolysis method are claimed. The racemization has previously been achieved only by chemical or physiochemical methods. In accordance with the invention, it is carried out with a microrganism from the genera *Achromobacter*, *Flavobacterium*, and/or *Alcaligenes* or with an enzyme formed by such a microorganism, or with the enzyme aminolactam racemase. Microorganisms from the genera *Cryptococcus*, *Candida*, and/or *Trichosporon* can be used as hydrolytic microorganisms; enzymes formed from such microorganisms or the enzyme L-α-aminolactam amidohydrolase may also be used. [DOS 2163018; Toray Industries, Inc., Tokyo]

[PR 55 IE—I]

Agents for the extermination of rodents contain trialkylphenols *(1)*. They are particularly suitable for use against rats, and are characterized by a cumulative effect. Phenols with *tert*-alkyl substituents are preferred; these can be used alone or in combination with agents for reducing blood platelet formation and for increasing capillary permeability and blood pressure or in conjunction with anticoagulants

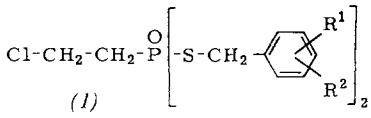

(1)

R = *sec*-, *tert*-alkyl (C_3—C_6)

for the formulation of the bait. [DOS 2145907; Imperial Chemical Industries Ltd., London]

[PR 86 IE—N]

Esters of phosphonodithiolic acids *(1)* can be used to regulate the abscission of fruits. They cause simultaneous ripening of all unripe fruits (berries, stone and kernel fruits, nuts, citrus fruits) without causing leaf fall or resin flow in fruit


(1)

R^1 = H, Cl, CF_3, CN, CH_3, C_2H_5, OCH_3, OC_2H_5;
R^2 = H, Cl, CH_3, OCH_3

trees. They are regarded as practically nontoxic to warm-blooded animals. [DOS 2144926; CIBA-Geigy AG, Basel]

[PR 85 IE—N]

BOOK REVIEWS

Gmelins Handbuch der anorganischen Chemie (Gmelin's Handbook of Inorganic Chemistry). 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., Germany. Eighth fully revised Edition.

System No. 61: *Silver*, *Part A 3*. Chemical behavior. Detection and determination. Toxicity. Colloidal silver. Principal editor: *Karl-Christian Buschbeck*. 1971. xi, x, 224 pp., 14 figures, Balacron DM 281.—.

Whereas the first two volumes of Part A[1] dealt with the history, geochemistry, and occurrence and the preparation and physical properties of silver, the present volume is concerned with the chemical behavior of the metal and its ions, their detection, and their determination. A brief chapter is devoted to the toxicity of the metal and its compounds and to the treatment of acute silver poisoning. The closing chapter on colloidal silver, which covers 41 pages, is very long; the most important part of this section describes the hydrosols. The data on organosols, aerosols, crystal sols, vitreosols, and silver mirrors are not very comprehensive.

A topic of special importance to the processing of metallic silver is the scaling phenomena that occur on contact with halogens and chalcogens. One would have expected this chapter to contain a section giving condensed data on scale removal. The behavior of silver toward the other elements and their compounds and toward less well-defined substances such as "open air", "kitchen atmosphere", "laboratory atmosphere", or foodstuffs (*e.g.* coffee, tea, must, wine, *etc.*) has also been very intensively studied,

as one might expect from the wide range of uses to which silver is put. A surprising result is that a 1955 Oberingelheimer white wine dissolved 30 mg of silver/m^2 in 7 days, but it is reassuring to find that this had no adverse effect on the quality of the wine! Moreover, silver is practically non-toxic, both as the metal and in the form of the ion. There is thus no reason against the use of silver goblets. Silver compounds are toxic only when taken orally in large quantities. There are, however, a series of special silver compounds particularly complexes, that exhibit considerable toxicity; these include the sodium dithiosulfatoargentate formed during the fixing process in photography.

In the sections on the behavior of Ag^+ and Ag^{2+} ions, it is interesting to note the large number of recent studies on Ag^{2+}. The plan of the chapter on detection and determination is very successful, and ought to be retained. The only criticism concerns the presentation of the references to the survey of the most sensitive reactions for silver (p. 107), which should have been given individually.

The literature has been evaluated up to and in some cases beyond 1969. The contents will be of interest not only to chemists and physicists, but undoubtedly also to the silver-processing industry.

System No. 61: Silver, Part B 2. Compounds with bromine, iodine, and astatine. Principal editor: *Rudolf Keim.* 1972. vi, xviii, 481 pp., 118 figures, Balacron DM 578.—.

The second volume of Part B completes the treatment of the silver halides, of which the silver fluorides and particularly silver chloride occupied most of the first volume[2]. Though there are very few compounds in the silver-bromine system (only AgBr and $Ag_mBr_n^{(m-n)+}$ are known, while the Ag_2Br and $AgBr_2$ postulated earlier do not exist), the discussion of this system occupies 185 pages.

The reason for the almost countless investigations is the importance of silver bromide to the photographic process. As can be seen from the many very recent references cited, the problems concerned with the effects of light have not all been solved. Considerable space is occupied by the description of structural and crystallographic properties, since crystal faults are of decisive importance to photographic sensitivity.

The only silver-iodine compound whose existence has been satisfactorily demonstrated is AgI. This exists in three modifications at normal pressure. Three high-pressure modifications are also known. As in the case of AgBr, the crystallographic properties are very important to the use of this compound in photography, and have therefore been very extensively studied. The high-temperature form of AgI exhibits good electrolytic conductivity, and is used as a solid electrolyte.

In a departure from the Gmelin system, the alkali metal and alkaline earth metal double compounds with common anions, such as KAg_4I_5, are each described in this volume after the corresponding simple silver compound.

Industrial importance is again the reason for the intensive investigation of colloidal silver iodide, which is used as aerosol and hydrosol. AgI hydrosols are also important as model substances for investigations on colloid-chemical behavior in general.

The silver-astatine system occupies only a few lines. A final chapter is devoted to the applications of the photochemical decomposition of silver halides. However, this treatment is confined to the explanation of fundamental concepts and a list of examples from recent literature.

The readability of the text is enhanced by the fact that as in some of the other recent volumes, contrary to earlier practice, the references are collected at the end of each section. The literature is evaluated up to mid-1970, and even more recent publications are also mentioned in a few cases.

Eckehard Fluck [NB 114 IE]

[1] Cf. Angew. Chem. internat. Edit. *10*, 204 (1971).
[2] Cf. Angew. Chem. internat. Edit. *11*, 69 (1972).

Analyse von Tensiden (Analysis of Surfactants). By *H. König.* Springer Verlag, Berlin—Heidelberg— New York 1971, 1st Edit., vii, 239 pp., 125 figures, stitched DM 58.—.

Ten years have now elapsed since the appearance of "*Hummel*". It was with some eagerness, therefore, that practical workers awaited *König*'s book; however, their hopes have been disappointed. Nevertheless, the book may be a welcome aid to newcomers to the field who wish to acquire a general grasp of the subject. The arrangement of the subject matter is such that anionic, amphoteric, nonionic, and cationic surfactants are discussed in order. For each class of surfactants, the separation methods are described first, and these are followed by the methods of identification. The sections on ion-exchange methods and the detailed description of paper and thin layer chromatography save a tedious search in the widely scattered literature. A chapter then deals with methods for the quantitative determination of surfactants.

As far as the identification of the separated species is concerned, the reviewer feels that the chapters on IR spectrometry present no essential advances over those in "*Hummel*". The spectra show, moreover, that the author has not yet a really good IR preparation technique (*e.g.* pressing the substances between two rock salt plates). NMR spectroscopy offers very little advantage over IR spectroscopy, which yields its information more rapidly and more cheaply (exception: ethylene oxide-propylene oxide mixed condensates).

In the quantitative part, considerable space is devoted to the author's own publications on the investigation of the half-esters of sulfosuccinic acid. On the other hand, practical workers will note the absence of guidance on the investigation of ether sulfates of fatty alcohols and alkylphenols, which are more important surfactants.

Finally, a word of caution: It has evidently escaped the author's notice that the "Comprehensive separation procedure" that he proposes (p. 43 *et seq.*) cannot be successful, since fatty alcohols and their ethylene oxide condensates cannot be extracted with ether in the presence of sulfonated surfactants. An inaccuracy in the text is that the liquid obtained by ion exchange is normally referred to as a filtrate, and not as an eluate. Confusion arises from the fact that the terms eluate and elute are occasionally also used in the normal sense.

Reinhold Wickbold [NB 119 IE]

Carotenoids. Edited by *O. Isler.* Birkhäuser Verlag, Basel—Stuttgart 1971, 1st Edit., 932 pp., numerous figures (some in color) and tables, bound Sw. Fr. 118.—.

The editor of the present book, which is in English, defines its aims in the introductory chapter. It is intended, as a continuation and extension of the monograph on carotenoids published by *Karrer* and *Jucker* in 1948, and partly

also of *Goodwin*'s "The Comparative Biochemistry of the Carotenoids", to summarize the results of chemical and biochemical research during the last two decades. The literature is covered up to about the middle of 1970. The book is in the form of a joint work by several authors. The editor, *O. Isler*, who is well known as the initiator of the first industrially used vitamin A synthesis for Hoffmann-La Roche, has managed to obtain the services of distinguished university research workers as well as workers from his own group as authors of the various sections.

In agreement with the dual aim, Sections II—VI deal mainly with chemical results, and Sections VII—XI mainly with biochemical results. Thus Chapter II describes the natural occurrence of carotenoids in plants and animals, and is thus closely related to Chapter VII, in which the biosynthesis of the carotenoids in these organisms is discussed in detail. Chapter III presents a survey of isolation methods, reactions, and relationships of the carotenoids with one another. The centerpiece of Chapter IV, spectroscopic methods, consists of comprehensive tables of NMR spectroscopic and mass-spectrometric data. Chapter V deals with stereochemistry, from *cis-trans* isomerism to the absolute configuration of chiral groups. A special appendix explains the application of the *R* and *S* convention.

Chapter VI will undoubtedly be of the greatest use to the preparative chemist. There he will find all the known total syntheses of carotenoids, as well as the syntheses of the fragments used, arranged according to synthesis schemes and summarized from time to time in tables. The thoroughness with which even the entire patent literature has been evaluated and arranged is unusual. In the past it was difficult to obtain a survey even of synthesis methods, since a large proportion of the research results has been published only in patents, and is widely scattered.

Chapter VIII, under the heading "Metabolism" deals with the degradation and transformation of the carotenoids in the organism; a separate section is devoted to the carotenoid-protein complexes, which are steadily gaining in interest. The function of the carotenoids and their metabolites are discussed in Chapter IX. The most important metabolite, vitamin A, is the subject of a separate Chapter X, where among other things, its largely verified role in the process of seeing and its as yet unexplained action mechanism in other parts of the body are discussed. The practical use of carotenoids as coloring agents and provitamins in foods and animal feeds is discussed in Chapter XI.

All the known naturally occurring carotenoids are listed in Chapter XII, together with literature references. However, the principle according to which they are arranged is to be found, not here, but in Chapter I. A suitable guide would be helpful where time is short.

The book is completed and rounded off by the IUPAC recommendations on nomenclature.

Despite the difference in style and approach in the various articles, they all have one thing in common, *i.e.* the critical care with which a large volume of material has been handled. Spot checks failed to reveal any serious omissions from the references. The book is strongly made and almost free from printing errors.

International cooperation has resulted here in a book that satisfies even high expectations, and that will, in a short time, become part of the essential equipment of all laboratories concerned with research on natural products and polyenes.

Wilhelm Sarnecki [NB 120 IE]

Progress in the Chemistry of Fats and other Lipids, Vol. 11. Edited by *R. Holman*, Pergamon Press, Oxford 1971, 1st Edit., xiii, 424 pp., numerous figures and tables, bound £ 11.00.

The present volume consists of several self-contained chapters on quite different subjects. The range of subjects in this volume is thus particularly wide, in contrast with some earlier volumes. Thus the chapter "Phospholipids, Liquid Crystals, and Cell Membrane" by *R. M. Williams* and *D. Chapman* deals with the physical properties of phospholipids and phospholipid-solvent systems and the consequent possible functions of phospholipids in biological membranes. In the two articles "Chemistry and Metabolism of Fatty Aldehydes" by *V. Mahadevan* and "The Chemistry of Sulfolipids" by *T. H. Haines*, the emphasis is placed on the chemical properties, the structural elucidation, and the synthesis of the substances of this class, for which these are the first detailed surveys. *C. R. Smith, Jr.*, in "Occurrence of Unusual Fatty Acids in Plants", presents an exhaustive synopsis of the structures of all fatty acids found in plants that do not have the polyallyl structure. In the article "Insect Lipids", *P. G. Fast* discusses both the composition and structure and the metabolism of these substances, and leads over in this way to the purely enzymatic section by *R. G. Jensen*, "Lipolytic Enzymes". This article describes the occurrence, the isolation, and the properties of the lipases that break down monoglycerides or triglycerides. There is also a chapter on the very topical subject "Pesticide Residues in Fats and other Lipids", by *A. M. Parsons*.

As in the earlier volumes, the author has succeeded in obtaining outstanding specialists in each of these fields as authors. This is reflected in particular in the excellent arrangement and the understable language. The volume will be of great interest not only to readers seeking an introduction to the special fields, but also to specialists who wish to brush up their knowledge. The extensive lists of references with all the articles also provide an opportunity for further study of the material discussed in the primary literature.

The favorable overall impression made by this volume is unfortunately weakened by the fact that apart from a very few references from 1970, some of the articles cover the literature only up to and including 1968, and others up to and including 1969. In the chapter by *A. M. Parsons*, the references listed stop at the end of 1967. Thus depending on the particular chapter, the literature from the last two to four years is missing, and the book is thus not as up-to-date as it might be. In the interests of the series as a whole, the articles in the later volumes should close on a single date and should be published quickly.

Wolf-H. Kunau [NB 124 IE]

Inorganic Titrimetric Analysis—Contemporary Methods. Vol. 1. By *W. Wagner* and *C. J. Hull*. Edited by *L. Jordan*. Marcel Dekker, Inc., New York 1971. 1st ed., xii, 225 pp., bound $ 13.50.

The book, which is described in the preface as unconventional, aims to provide the chemist who is occasionally faced with the need to determine an element (or simple inorganic ions and compounds, such as azide, hydrazine, cyanide, or dithionite) with a suitable titration method in a form such that it can be carried out in a normally equipped laboratory (*e.g.* electric and photometric indication, coulometric titration) with good prospects of success.

It also aims to eliminate the need to consult handbooks of analytical chemistry or the indexes of analytical periodicals or abstracting journals before carrying out such work.

To live up to this very pragmatic aim, well known and currently used titration methods, acidimetric, complexometric, precipitation, and redox methods are described for the determination of each element; their suitability, selectivity, accuracy, and susceptibility to interference are indicated, and the necessary aids are mentioned. Details of procedures are deliberately omitted, and the reader is referred instead to a number of important recent publications in every case.

The arrangement of the book, in which convenience is the main consideration, is clear, as is that of each of its chapters. It is based on the periodic system of the elements (including the transuranium elements and the inert gases), and a survey of classical (pre-1950) and up-to-date (mostly post-1960) possibilities is followed in every case by brief descriptions of the selected methods.

The attempt to provide the chemist who is not primarily an analyst with a volumetric vade mecum may be said to have been accomplished in full. The book can only be recommended to all amateur analysts, but is also a rich source of information for the professional analyst.

Günther Kraft [NB 133 IE]

Polymer Science and Materials. Vol. 1. By *A. V. Tobolsky* and *H. F. Mark*. John Wiley and Sons, Inc., New York–London 1971. 1st ed., x, 404 pp., numerous figures and tables, bound £ 10.05.

The book is intended mainly for younger students and for scientists and technologists wishing to enter the field of polymer science or seeking a first introduction. The material presented covers a wide field. The present first volume of the planned two-volume work deals with the essential physicochemical principles of polymers in solution, as well as with the physics of the solid state of synthetic macromolecules, and finally in three chapters with the technical properties and the processing of rubbers, plastics, and fibers.

This breadth of material was possible only through the deliberate omission of all mathematical derivations. One result of this is that the numerous formulas used occasionally appear rather abruptly. It would have been preferable in such cases to present plausible explanations for the most important formulas. The aim of providing such an urgently needed book for the beginner has therefore been achieved only in part.

In addition to providing an introduction to polymer science, the book also strives to consider the fundamental science and the industrial application from a common standpoint. It may be regarded as successful in this respect, and it thus stands out from other works, which favor either one point of view or the other. The book benefits from the fact that the conception is essentially determined only by the two principal authors.

However, the level is not always constant. A very good and enthusiastic introduction is followed by a chapter on molecular weight and molecular weight distribution that is unsatisfactory and out of date with regard to material. Solid knowledge is presented in most of the chapters. Two contributions can be described as outstanding. These are the chapters "Equilibrium Polymerization" and "Liquid and Plastic Crystals". This last article in particular is unconventional, opens up new aspects, and should provide a stimulus even to the specialist in the polymer field.

Walther Burchard [NB 137 IE]

Molekulare Prozesse des Lebens (Molecular Processes of Life). By *D. E. Green* and *R. F. Goldberger*. Springer-Verlag, Berlin–Heidelberg–New York 1971. 1st ed., x, 240 pp., 93 figs., bound DM 38.—.

The aim of this book is unusual, *i.e.* the description of selected fundamental biochemical processes in living systems and of important molecular reaction courses that are identical or very similar in numerous organisms in very different stages of development. By the omission of individual facts and the stressing of common fundamental mechanisms, the reader is shown the principle of biochemical life processes and made aware of the essential points.

In addition to the structure of the cell and its components, the discussion deals mainly with enzymes and their mode of action, control mechanisms of cell metabolism, and the structure and function of macromolecules (polysaccharides, proteins, nucleic acids, phospholipids). A very large amount of space is rightly given to the discussion of the energy balance of the cell (energy-supplying processes, energy-dependent syntheses, and energy transfers). However, the chapter "DNA, RNA, and Protein Synthesis" is very brief and the material is very greatly simplified in places; stronger emphasis in this area would surely have been desirable in view of the central position within the field of molecular biology. The structure of the book is such that it contains no data on methods and literature. The translation from the English is good. The book is written in an easily understandable manner, the material is clearly and logically arranged, and details and special knowledge are mentioned only where they contribute to a better understanding of fundamental biochemical mechanisms.

This book is thus not intended as a conventional textbook. It is aimed at a broader readership, and may be regarded as a very successful attempt to present fundamental molecular processes in living systems clearly and understandably.

Jürgen Niessing [NB 134 IE]

Lactic Acid. By *C. H. Holten*, with chapters on Biochemistry (by *D. Rehbinder*) and on Analytical Chemistry (by *A. Müller*). Verlag Chemie, Weinheim 1971. 1st Edit., pp. 566, 98 figures, 181 tables, bound DM 135.—.

The book is the first large monograph on lactic acid to be written. It covers all aspects of the subject: history; applications; physical and chemical properties; derivatives; biochemistry; and analytical chemistry. Its writing has been supported by an international research association of four European producers of lactic acid. This association (called Stichting Ilra) has further assisted by making inside information on the subject available to the authors.

The literature is covered up to June 1968. About 3000 publications have been studied. Publications in languages not commonly understood have been evaluated from the original and not from summaries written in another language. The over 2000 publications entered as references have been selected critically, so that the book is not a mere compilation. References are with full titles and the number of pages of each publication is given. Among the references is a number of dissertations, some of which have remained unpublished.

The book has been written with great care over a period of eight years, and its usefulness cannot be questioned. The specialist will study it again and again. Apart from this, and perhaps contrary to what many would expect, most chapters are also interesting reading to chemists working outside the lactic acid field. The reviewer believes that the book will retain its value for many years. It is therefore recommended to every chemist or organization working with lactic acid or its derivatives, as well as to all organic chemical laboratories in general.

Niels Clauson-Kaas [NB 154 IE]

Properties of Polymers. Correlations with Chemical Structure. By *D. W. van Krevelen*. Elsevier Publishing Company, Amsterdam—London—New York 1972, 1st Edit., xi, 427 pp., numerous figures and tables, bound, $ 22.—.

The book deals with the thermophysical properties of polymers, their behavior in mechanical and electrical force fields, transport phenomena such as flow processes, diffusion, and permeation, and crystallization and degradation processes. The discussion is therefore based on the chemical constitution of polymers, with particular emphasis on the additivity principle. The author demonstrates most convincingly, drawing extensively on his own work, how it is possible to calculate, or at any rate estimate, many of the characteristics of a polymer from the physical data for the monomers, and even for the groups of molecules forming them. For this procedure the book offers a large number of clearly arranged tables and diagrams with the various monomer and polymer characteristics. At the same time, the author points out the limitations of the additivity principle, *e.g.* in the case of strength data and in the domain of crystalline polymers.

Quantitative relationships are given without derivations —the reader will find detailed references to the literature— but in a form such that they can be used directly for calculation. The many approximation formulas and rules of thumb should prove particularly useful in practice. Applications are illustrated in the form of problems, and the reader can test his knowledge by referring to the solutions. Whereas defined physical properties always receive detailed treatment, technological characteristics such as readiness to pick up an electrostatic charge, slip-stick behavior, or abrasion resistance take up relatively little space, no doubt a clear sign of the limited extent of our present knowledge concerning these aspects, despite their practical importance.

The book is obviously not intended primarily as an introduction to polymers: for example, the reader is assumed to possess a knowledge of the most important measuring methods. Anyone acquainted with the field will, however, find the book very much to his liking, for it is concise, well formulated, clearly laid out—each chapter begins with a summary of its contents—and the printing is of a high standard. In short, this is a monograph that will not only be read, but also used.

Ulrich Zorll [NB 125 IE]

The Condensed Chemical Dictionary. By *G. G. Hawley*. Van Nostrand Reinhold Comp., London 1971, 8th Edit., ix, 971 pp., bound £ 13.75.

It should be stated at the outset that this "dictionary", which first appeared over 70 years ago has the character of a handbook listing materials (defined compounds, commercial products, alloys), specialized terms, and potted biographies of prominent chemists from the past. The book contains a total of 18000 entries.

The explanations are sufficiently detailed and lucid. Against compounds the reader will find—where known—synonyms, linearized structural formula, properties (color, state, m.p. and/or b.p., solubility), occurrence or preparation, transportability, and hazards (toxicity, flammability). The composition of commercial products is described and the supplier is named. A list of suppliers is given at the end of the book. Examination of this list shows that it consists almost exclusively of American-based companies. The brief description of "leading" scientific societies are restricted to American organizations, and the biographies of deceased chemists fail to include Nobel Prize Winners such as *Wallach*, *Werner*, *Willstätter*, and others. The technical terms listed are intended primarily for the practical chemist. One does not find the specialized terms used in theoretical chemistry and process technology. The 8th edition devotes particular attention to chemical and biological aspects of environmental pollution and its control.

On the inside cover the book is recommended as an indispensable aid to all chemists. This assertion may be questioned, in view of the shortcomings referred to. However, anyone interested in the American market will undoubtedly find useful information in it. The practical chemist, too, may find this book a useful addition to his reference library.

Christian Weiske [NB 126 IE]

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The Origin of Life[**]

By Mella Paecht-Horowitz[*]

The theory of the evolution of the species, which is today widely accepted, requires a starting point. It is postulated that the biological starting point could have emerged only if chemical evolution had preceded it. Experiments are described which show the formation of organic substances from inorganic gases under conditions which prevailed on earth in the prebiotic era; also demonstrated is the polymerization of such organic substances into biological macromolecules. Hypotheses are discussed whereby these macromolecules could be transformed into dynamic structures which might finally lead to self-reproduction.

1. Introduction

With the development of space research, the problem of the "Origin of Life", although a very ancient one, has suddenly become extremely modern. Researchers are very anxious to detect whether there is any form of life in extraterrestrial space. As it is most improbable that extraterrestrial life forms (if any!) would be the same as those on our planet, it has become necessary to define life, to determine its characteristics and how it appeared.

There are many definitions attempting to describe life. One enjoying widespread acceptance by biologists is that a system is "alive" when it is able to reproduce itself at the expense of its internal energy; in other words, when it is able to self-reproduce with the help of its inbred memory and mechanisms.

But the problem of the origin of life is already mentioned in the earliest scriptures. The search for the "starting point" was one of the first problems ever treated by the philosophers of ancient times. The scholars of India, Babylon, and Egypt, under the strong influence of religious legends and traditions, believed that life started by autogenesis, as a result of the creative will of supernatural powers.

The Greek philosophers, from about 600 B. C. onwards, approached the problem by "scientific" methods. Nevertheless, they believed strongly in autogenesis and brought forth numerous experiments intended to prove this theory. This belief in autogenesis continued throughout the Middle Ages and into Modern Times. *Francis Bacon*[1], *Descartes*[2], and their contemporaries considered spontaneous generation as beyond question and it was only in 1668 that *Redi*[3] described a series of experiments proving that flies can generate only from flies' eggs. Still, even *Redi* believed that though flies indeed generated from eggs of their species only, autogenesis might take place in other cases. The final definitive proof that a species cannot generate save from another specimen of its own family was provided only by *Louis Pasteur*[4–10]. Yet this brings us back to the original question, namely, if an organism can be created only by another organism, how did life start at all?

Nowadays there is just one logical answer to this question, namely, that chemical evolution must have preceded biological evolution, and that the latter could have ensued only as a result of the former. Actually, this was already recognized by *Darwin* who stated that if, at the present time, a protein substance capable of experiencing further, more complex transformation were created, it would be

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[**] It was intended that this discussion be written by Professor *Aharon Katzir-Katchalsky* and myself. Because of his tragic death at the Lod Airport massacre, I have had to write it alone; all I can do is dedicate it with deep sorrow to his memory—the memory of a great scientist, an outstanding teacher, and a most wonderful personal friend.

consumed or absorbed—which could not happen in the period preceding the formation of living creatures[11]. This statement brings us face to face with the first difficulty in the investigation of the origin of life—primordial formation of life under natural conditions is now impossible due to the very fact of the existence of life. This impossibility leads us into the situation that whatever experiments we conduct, however conclusive they may be, can only show possibilities that life could have started under certain specific conditions; we shall never be able to know precisely the actual conditions under which life started. Even if—by some very unfortunate event—all life on earth were to be extinguished, save for some scientist remaining to study the eventual new formation of life, the situation would not be the same as in primordial times. Earth, now deprived of life, would be like a person who has lived but is now dead, whereas in the primordial era it was like an unborn, even unconceived child.

2. The Primordial Broth

What do we know about the period preceding life on earth? According to geochemical investigations, life started on earth between one and two thousand million years ago. But whereas up to two thousand million years ago the atmosphere contained no oxygen, a thousand million years ago it was already very rich in that element. The interval between these times is the transition period, during which life on earth started. With the development of life, the atmosphere became more and more enriched in oxygen, and the more oxygen there was, the more highly developed creatures emerged.

Although nowadays lack of oxygen might stop life, it was apparently its very absence which enabled life to be formed in the prebiological era. Because of this feature, the amount of short-wave radiation reaching the surface of the earth was much greater than it is now. The 30 km deep ozone screen presently surrounding the earth considerably increases the wavelengths of radiation reaching its surface. Thus the possibilities for abiogenic photochemical syntheses were far greater than they are now. Of course, the lack of oxygen created a situation in which reduced carbon compounds could not become highly oxidized; living organisms did not exist, thus precluding the synthesis of a vast number of organic compounds by metabolic processes.

Because of all this, and because the period we are discussing left practically no geological traces, it is extremely difficult to reconstruct prebiotic situations in the laboratory, especially if these situations have to stay constant for prolonged periods of time. Nevertheless, some experiments worth mentioning have been carried out.

3. Prebiotic Synthesis

3.1. Formation of Organic Compounds under Prebiotic Conditions

Before going into details it should be mentioned that not everyone is of the opinion that the origin of life is a subject which should be treated at all by physicists or chemists. Those who hold this negative viewpoint believe that physical methods are *a priori* antihistorical, as they deal with situations which tell what can be predicted, according to physical laws, when the starting conditions are known. Thus they are indicated for predicting the future, and not for reconstructing the past. Not only do the laws of physics not teach us anything about the past, but the laws of thermodynamics tell us that natural phenomena tend to approach an equilibrium state and the description of a state does not include anything about the way it has been reached. What physicists and chemists can do is build models and test to what extent these models are consistent with the findings of biologists, geologists, anthropologists, and cosmologists. All these efforts might together come up with the right answers. The following experiments give some of them:

In 1955 *Miller*[12] passed electric discharges through a gaseous mixture of methane, ammonia, hydrogen, and water vapor and thus obtained various organic compounds, notably amino acids. By the same method, and also adding phosphoric acid to the reaction mixture, *Gulick*[13] obtained high energy phosphorus compounds similar to phosphocreatine. *Scott*[14] even synthesized complicated compounds like porphyrins in this way. *Oró* and his collaborators[15–19] heated simple hydrocarbons with hydrocyanic acid and its derivatives—hydrocyanic acid was believed at that time (1961) to have been carried to the earth by comets—and obtained amino acids, peptides, aliphatic acids, purine and pyrimidine bases, imidazoles, and pentoses. In 1962, *Palm* and *Calvin*[20] bombarded methane, ammonia, water vapor, and hydrogen with high energy electrons and obtained the same products as *Oró*'s group, and in addition HCN. Thus it was no longer necessary to postulate that this substance came from extraterrestrial sources. The formation of HCN is, according to certain investigators in this field, extremely important, because it and its derivatives might have been some of the key components in prebiological synthesis, as they are dehydrating agents *par excellence*. Later, *Ponnamperuma* and his collaborators[21,22] described the formation of ATP, still under prebiotic conditions, and *Bar-Nun et al.*[23] again produced amino acids and peptides from inorganic gases with shock waves as energy donors.

All these experiments show clearly that the formation of organic substances out of inorganic ones, even in the absence of oxygen, is possible and one may safely assume that gases like those mentioned above were the prebiotic molecular compounds on earth. There is good reason to believe that the first organic substances were formed from them with any of the natural energy sources then available.

Yet the way from here to a living cell, or even only to an organized macromolecule with a well defined sequence of monomers, is still very long.

3.2. Formation of Macromolecules under Prebiotic Conditions

It is logical to assume that life orginated in several stages. The first would be the formation of organic substances as described in the previous section, the second would be the arrangement and combination of monomers into macromolecules, the third would be the transformation

of such a lifeless macromolecule into a living one, and finally, we would have the evolutionary development of higher living forms out of the very simple ones.

There are investigators who believe that the second stage preceded the first one. *Mathews* and *Moser*[24] showed that when HCN is mixed with dry NH_3 and exposed to an electric discharge, protein-like molecules are obtained, which, on hydrolysis, give amino acids. Yet up to now, most investigators try to build biopolymers out of their monomeric units. *Schramm et al.*[25] showed that when metaphosphate esters of various compounds are heated in non-aqueous media, high polymers of the respective compounds are obtained. In this way they prepared polynucleotides, polypeptides, and polyglycosides. *Schramm* relates these findings to prebiological synthesis by the fact that orthophosphates are not stable above 300 °C; therefore he assumes that large deposits of condensed phosphates existed in water-free regions after the earth cooled down. These phosphates might have been esterified by reactions with organic compounds and produced condensations inside coacervates as has been proposed by *Oparin*[26], or in other aggregates protected by water-proof membranes.

Oparin's reasoning that condensations occurred inside coacervates was based on the following set of experiments: When adenine is polymerized *in vitro* in a polypeptide medium droplets, called coacervates, begin to separate out from the solution as soon as the molecules reach a certain size. On formation of the droplet the reaction equilibrium experiences a sharp shift towards synthesis[27]. Thus *Oparin* reasons that, if prebiological systems were subject to the same physical rules as present-day systems, production of two polymeric species would be followed by formation of a coacervate inside which reaction would continue.

We have here an assumption which should be approached carefully. While we have to assume equal laws of nature in the prebiotic era and now, for no working hypothesis would otherwise be possible, this biases our concepts of structures and forms of life and makes us project the conditions of the present into the past. To do this might be perfectly logical, as there is no reason to believe that the prebiotic chemical and physical laws were different from those of today; but we should not forget that the validity of this argument has not been proved.

Another experiment which strongly supports *Oparin*'s theory is that performed by *Evreinova et al.*[28]. This group showed that when droplets formed from gelatin and gum arabic are present in an amino acid medium, the amino acids become concentrated ten- to hundred-fold inside the coacervates. This is true of other components also, the high concentrations depending on the composition of the droplet as well as on the type of the substance absorbed. Tempting as *Oparin*'s theory might be, we have to keep in mind that such a droplet cannot serve as a convincing model for a living system, as a state of equilibrium is very soon set up between the droplet and the surrounding medium. The droplet reaches a thermodynamically stable state and becomes thus a static system.

Yet the characteristics of the stability of a living system is that it is in a state of flux and produces a steady-state system. Throughout the whole of its life any cell or multicellular organism is in a state of continuous interaction with its environment—an interaction known by the biological term "metabolism". In physical terms, the case of the droplet in thermodynamical equilibrium could be defined as a state in which there is no change in free energy ($dF=0$), while in a living organism or cell the change in free energy occurs continuously, but at a steady rate ($dF=\text{const}\neq 0$). When a living cell reaches a state where $dF=0$, the cell has ceased to live and has become a dead cell.

However, steady state conditions can be created in the laboratory. The problem is to create systems which will work in the expected way. One of the most important properties required is that the system should be able to grow in a solution of substances expected to have been present in the "primeval broth" of the earth. For instance, if we had a polymerization reaction linked to redox and phosphorylation processes, this would require the coacervate droplets which were previously developed to be capable of synthesizing polymers and of creating conditions under which the redox reaction and the polymerization linked to it could proceed more quickly than in the external medium. Such conditions could easily have arisen in droplets able to absorb strongly from the surrounding medium, so that the droplets would contain a constantly increasing concentration of substances which would act as catalysts for further polymerization. Such continuous polymerization would increase the mass of the droplet and the reaction would go on faster and faster, leading to a sort of mechanism which could explain the first catalytic reactions, analogous to metabolic reactions.

Furthermore, one could imagine that after reaching a certain size the droplets would split up into fragments of identical consistency with the parent droplet and one would thus obtain some sort of division, analogous to cellular division, although the system would still not be alive.

Calvin[29] pointed out that the development of biological catalysts from such simple catalytic systems of coacervates could have emerged by natural selection. Such a selection would be possible only when the catalyst was incorporated into a synthetic system. If the catalyst was simply in solution, no selection could occur with respect to a specific reaction because individual components of a catalytically active system, when dissolved in the surrounding medium, might, in themselves, be almost entirely lacking in this activity. When selectively absorbed, however, they would combine within the absorption medium to form a catalytically active complex which would increase the rate of reaction relative to the surrounding medium. The readiness to form such a complex would be the very factor which could determine the flowing nature of the system, its dynamic stability, and its ability to grow. It is clear that the more suited the molecular structure of the complex is to its catalytic function, the more the system will maintain itself and the more it will grow and multiply.

The theory of the coacervates calls for already existing polymers which would interact with each other and would form the droplets. But as we do not know how these polymers could have been formed in the prebiotic era we have to look for some means of concentration of the monomers. As all biological reactions and also many of

the chemical ones proceed in aqueous solutions we have to assume, for reasons of continuity and equality of conditions, that the primary synthesis occurred in aqueous solution as well. We can imagine that some of the reactants, after having been formed, fell into the oceans where they were able to react with each other. However, the primary difficulty in imagining the polymerization process to have taken place in the free ocean lies in the extreme dilution of the system.

Bernal suggested that concentration of the products, which would be an absolute necessity for evolution, could be attained by adsorption on very fine clay deposits in marine and fresh water[30]. Following this assumption, we dissolved an amino acid adenylate—the starting material for protein formation in the living cell—in water at pH 7.8 and room temperature in the presence of finely dispersed montmorillonite. This mineral is a rather interesting clay. It consists of three-layered sheets of SiO_2—Al_2O_3, $Al(OH)_3$—SiO_2 (Fig. 1) and is able to swell, expanding

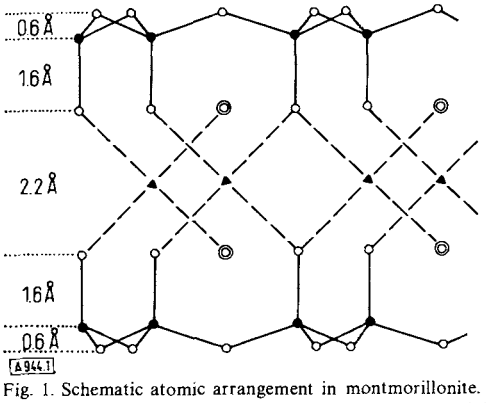

Fig. 1. Schematic atomic arrangement in montmorillonite. ○, oxygen; ◎, hydroxyl; ▲, aluminum; ●, silicon. The upper and lower layers are tetrahedral, the center layer is octahedral.

enormously in the process. We may therefore assume that monosheets of very large surface area are obtained at low concentrations. Furthermore, the aluminum ion may be replaced by other cations. In the particular montmorillonite we have been working with, every sixth aluminum ion was replaced by a magnesium ion[31]. Since aluminum is trivalent and magnesium divalent, this exchange produces strong negative centers arranged in a sort of lattice. These negative centers are presumably the active adsorption centers of the clay. While montmorillonite at pH 7 adsorbs neither amino acids nor adenylic acid, it strongly adsorbs the amino acid adenylates which undergo polymerization to polypeptides while in the adsorbed state. Polymerization in the absence of clay and in a homogeneous medium produces low molecular weight peptides having a continuous molecular weight spectrum and which are free of adenylic acid[32, 33]. Heterogeneous polymerization in the presence of montmorillonite, in contrast, results in a very interesting non-continuous distribution of molecular weights (Fig. 2)[34].

Not only is the molecular weight distribution different, the polymerization mechanism itself differs from that of homogeneous polymerization. While the latter mechanism involves a primary hydrolytic step and only the free amino acid is able to interact with a molecule of amino acid adenylate, the resultant free dipeptide released on hydro-

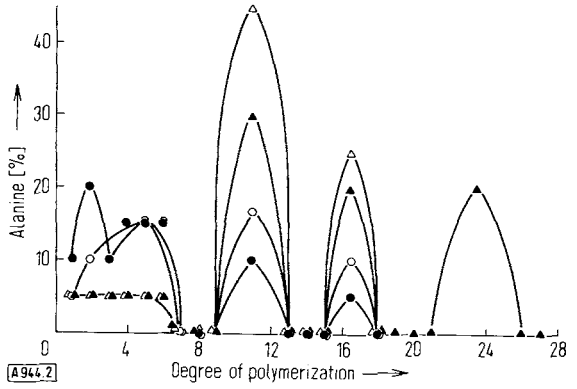

Fig. 2. Distribution of the molecular weights of polyalanines obtained when D,L-alanine adenylate is introduced into an aqueous solution at pH 8.5 in the presence of various amounts of montmorillonite ●, 20; ○, 80; △, 220; ▲, 480 mg montmorillonite/l.

lysis undergoing further reaction with another molecule of amino acid adenylate to give a tripeptide, *etc.*, the dominant reaction in heterogeneous polymerization is interaction between two active adenylates resulting in a still active higher peptide. The mechanism of homogeneous polymerization can be represented by the following scheme:

$$A \sim P \xrightarrow{h} A + P$$
$$A + A \sim P \xrightarrow{k} A_2 + P$$
$$A_2 + A \sim P \xrightarrow{k} A_3 + P$$
$$\vdots$$
$$A_n + A \sim P \xrightarrow{k} A_{n+1} + P$$

Where $A \sim P$ is the active amino acidadenylate, A the free amino acid, A_n the peptide of the n-th degree of polymerization, P free adenylic acid, h the hydrolytic constant, and k the polymerization constant.

Heterogeneous polymerization, on the other hand, can be represented as follows:

$$A \sim P + A \sim P \xrightarrow{k} A_2 \sim P + P$$
$$A_2 \sim P + A_n \sim P \xrightarrow{k} A_{n+2} \sim P + P$$
$$A_n \sim P + A_m \sim P \xrightarrow{k} A_{n+m} \sim P + P$$

The reaction scheme shows that homogeneous polymerization is a one-by-one step reaction and would therefore result in peptides having a continuous spectrum of chain lengths. Furthermore, we would not expect very high molecular weights since hydrolysis is necessary for the reaction to take place and is, in fact, the dominant reaction. In the case of heterogeneous polymerization, hydrolysis is not only unnecessary, but is actually almost completely suppressed by the protective action of the clay.

The fact that the peptides obtained by heterogeneous polymerization have a discrete molecular weight spectrum is very intriguing and we believe that it could explain some of the selectivity problems of the prebiotic era. From a purely chemical point of view, we have here a superposition of several reactions. The polymerization process liberates free adenylic acid which inhibits polycondensation by preventing the non-reactive ammonium group from dissociating. It is this dissociation with release of a proton which produces the highly reactive terminal amino group. Thus we can readily envisage that a pulse of rapid polycondensation will produce a high local concentration of acid molecules which will stop the process until the adenylic acid diffuses out.

After this diffusion a second pulse will occur which will again be stopped after several steps by the accumulated acidity. The joint operation of reaction and diffusion flows might very well give dissipative structures as described by *Prigogine*[35]. We shall see in Section 4 that such a combination of flows is very decisive also in structure formation. Incidentally, the pH range of about 4 produced by the accumulation of free adenylic acid most effectively stabilizes the amino acid adenylate, and this might be the reason for the protection of the adenylates from hydrolysis by montmorillonite.

While the main reason for the termination of homogeneous polymerization is hydrolysis, in the case of montmorillonite as polymerization template the reaction is terminated by transfer of the peptide chain from the phosphoric acid group to the ribose of the adenylate[31] (Fig. 3). In this case, the adenylic acid remains bound to the peptide, but the latter is no longer active and thus unable to grow and combine with other peptides.

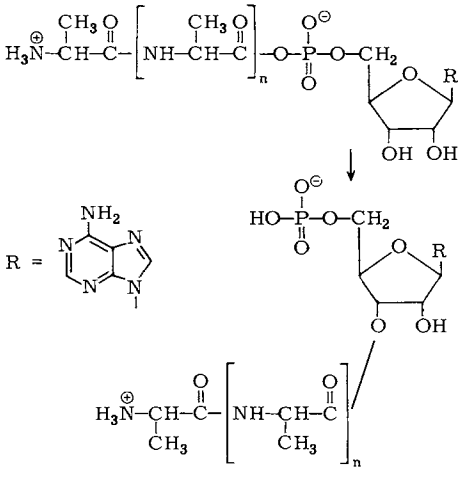

Fig. 3. The termination reaction in the heterogeneous polymerization of D,L-alanine adenylate.

But the importance of clays as related to prebiotic synthesis lies, in our opinion, not only in the fact that some of them are able to adsorb adenylates and thus produce local high concentrations of the reactants and specific chain lengths of polypeptides. It was again *Calvin*[23] who pointed out that the selection of chains of certain molecular weights from a large number of possibilities is typical of living processes, and here we have such a selection. Yet it seems to us that the importance of clays lies also in their various combination possibilities. Since the metal ions can be exchanged in the configurational layers themselves, not only can the adsorption capacities be varied, but also the spacing between active centers. This might bring about a sort of prebiotic template that might further produce a code, which, by due evolutionary development, could lead to the selective survival of such sequences which might ultimately become "alive".

Cairns-Smith[36] postulated that mica or other clays might have served as templates for prebiotic gene formation due to their regular configuration and spacings into which amino acids would fit. We would not go so far, because such a theory would require a rigid pattern of amino acid sequences. Our preliminary experiments on copolymerization of amino acid adenylates in the presence of montmorillonites have shown that indeed there are certain preferences, with some pairs of amino acids copolymerizing more readily than others, but even on the same clay there is a certain amount of fluctuation in this respect. In our opinion, clays by virtue of their various adsorption possibilities might bring the various reactants near to each other within a limited pattern, but the reactants would still have some degree of liberty to choose their interaction partners. Otherwise, we would always obtain the same sequences in copolymerization, which obviously is not the case. We believe that the well defined sequences of amino acids which exist nowadays in proteins were formed only later on, as a result of selectivity of survival processes.

There is another possibility which clays might offer. We have seen that important local pH changes occur in the course of the reaction. These changes allow us to speculate whether, under the right conditions in the presence of mixtures of suitable clays, adenylates of amino acids might not only be the forerunners of polypeptides, but at the same time also of polynucleotides. For many years researchers have asked themselves, what preceded what—the proteins the nucleic acids, or *vice versa? Eigen*[37] showed that for the formation of life, both were actually necessary. Figure 4 shows the formation of polyamino acid adenylate and the hypothetical formation of polyadenylic acid, with an amino acid still linked to one end of the molecule.

On paper at least, it is easy to see that both could be formed at the same time, starting with the same precursor. Yet while the formation of polypeptides has actually been observed[31] no polymerization of adenylic acid could be detected in the same circumstances.

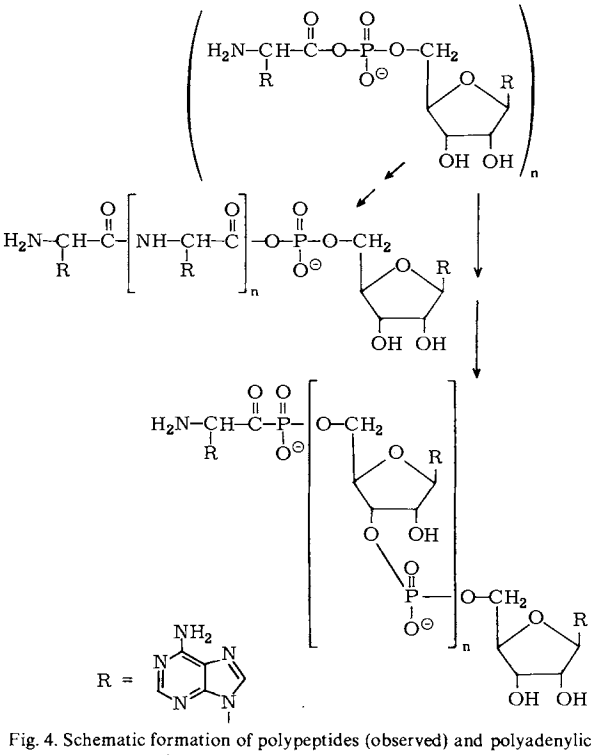

Fig. 4. Schematic formation of polypeptides (observed) and polyadenylic acid (hypothetical) from the same precursor.

3.3. Formation of Active Monomers under Prebiotic Conditions

Among the various catalytic properties of clays and minerals there is one which might have strong bearings

on prebiotic synthesis. We have seen in the previous section that amino acids must be activated in order to be able to polymerize. The need for activation of biomonomers for the polymerization process was pointed out by *Lipman* as long ago as 1941. In order to activate an amino acid, *i.e.* to transform it into a mixed anhydride with adenylic acid or with another nucleotide, the carboxylic group of the amino acid has to be in its free form and not in the ionized carboxylate form. Usually such is the case only at very low pH values, which, however, cause fairly rapid decomposition of ATP, the nucleotide donor of the mixed anhydride. Besides, it is unlikely that such low pH values (about 1—2) would occur in nature. Here another family of minerals, the zeolites, might provide a solution. Zeolites are alumino-silicate minerals well known in chemistry as molecular sieves. Some of them also exhibit very good ion exchange properties; hydrolysis produces a large number of $\geqslant$SiOH groups:

$$\geqslant SiO^{\ominus}Na^{\oplus} + H_2O \rightarrow NaOH + \geqslant SiOH$$

The SiOH groups would react with the amino acids under neutral conditions in the following way:

$$\{\geqslant SiOH + H_3N^{\oplus}—CHR—COO^{\ominus}\} \rightarrow \geqslant SiO^{\ominus}H_3N^{\oplus}—CHR—COOH$$

The latter form of the amino acid would be able to react with ATP to give the mixed anhydride which allows the amino acid to polymerize. This idea has been tested with an artificial zeolite called Decalso F[39]. Decalso F strongly adsorbs amino acids and ATP but the amino acyl compound formed is not adsorbed and passes readily into the aqueous phase. Since the amino acyl compound is hydrolyzed rather rapidly, its formation can be detected only by the increased rate of decomposition of ATP while the measurable content of amino acid remains constant. If montmorillonite, the "polymerization catalyst" is added, the free amino acid content also decreases due to polymerization, and after a certain period polypeptides are obtained with the same molecular weight distribution pattern as those produced when amino acid adenylates are polymerized in the presence of montmorillonite. Figure 5 shows the process; the starting point is adsorption of zwitterionic amino acids and ATP from the aqueous bulk solution by the zeolite and the final step is polypeptide formation on the montmorillonite, where the active anhydride formed on the zeolite transfers to the montmorillonite surface.

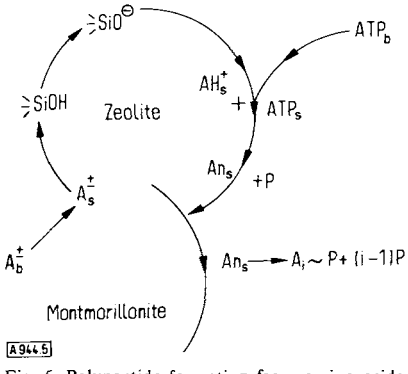

Fig. 5. Polypeptide formation from amino acids and ATP on zeolites and montmorillonites. $A^{\pm}$, amino acid; AH^{+}, free carboxyl form of the amino acid; An, mixed anhydride of amino acid and ATP derivative; $A_i \sim P$, polypeptide; P, free ATP derivative; the subscripts b and s mean that the amino acids are in solution and adsorbed, respectively.

4. Precellular Organization

Fox et al.[40] put a mixture of dry amino acids containing large amounts of aspartic and glutamic acid in the depression of a piece of lava; the lava with the amino acids was then placed in an oven at 170 °C, and after several hours the rock was removed and washed with hot 1% NaCl solution. The liquid contained large numbers of microspherical units, consisting of high polymers of amino acids. The same reactions can be observed when meteorites are used instead of lava. These microspherical units are called protenoids and they are able to swell or to shrink in hypotonic or hypertonic solutions respectively, although these responses are less marked than those of biocells. They retain their shape for an apparently indefinite time and when centrifuged at 3000 rpm retain their integrity. They also have sectionability properties and are stable even after division.

Later, *Fox* showed that the polymerization of amino acids can be accomplished at as low a temperature as 70 °C when polyphosphoric acid is present in the reaction medium[41]. Even orthophosphoric acid reduces the polymerization temperature, though less so than polyphosphates, provided the medium is completely anhydrous. *Young et al.* have shown that in the presence of the ethyl ester of polyphosphoric acids, the amino acids polymerize at 25 °C; on cooling the polymerization products slowly from 25—0 °C, they obtained protenoid microspheres[42]. These microspheres were able to coagulate and showed typical interactions with polymers of opposite charge. After interaction with a polymer of opposite charge such microspheres are seen to resemble a "blastule" with a double membrane under the microscope. pH, salt concentration, pressure, and temperature also have an effect on the morphology of the microspheres.

Formation of such microspheres requires a water-free reaction medium, which is contradictory to biological processes. Yet aqueous structure formation, based on physical phenomena, also exists.

As long ago as the beginning of this century, *Bénard* showed that when a homogeneous liquid is heated slowly at the bottom of its container certain geometrical structures are obtained at a certain critical temperature.

These structures, at first ring-like, become honeycomb-like on further heating[43-45]. The range of critical temperatures is very narrow, and with further increase in temperature, the liquid becomes homogeneous again. Figures 6 (a—c) show an oil at various stages of such a heating procedure[46].

The structures are the result of the reciprocal interaction of two types of flows, heat flow in an upward direction, and convective flow in a downward direction. Such phenomena can also be observed in crystallization processes. Often the individual crystals conglomerate into macroscopic cellular forms having a very regular structure. For the formation of these structures, various flow processes must take place; such structures could never be obtained in equilibrium states. They are dynamic structures, like those of living cells, but they are obtained by purely physical processes.

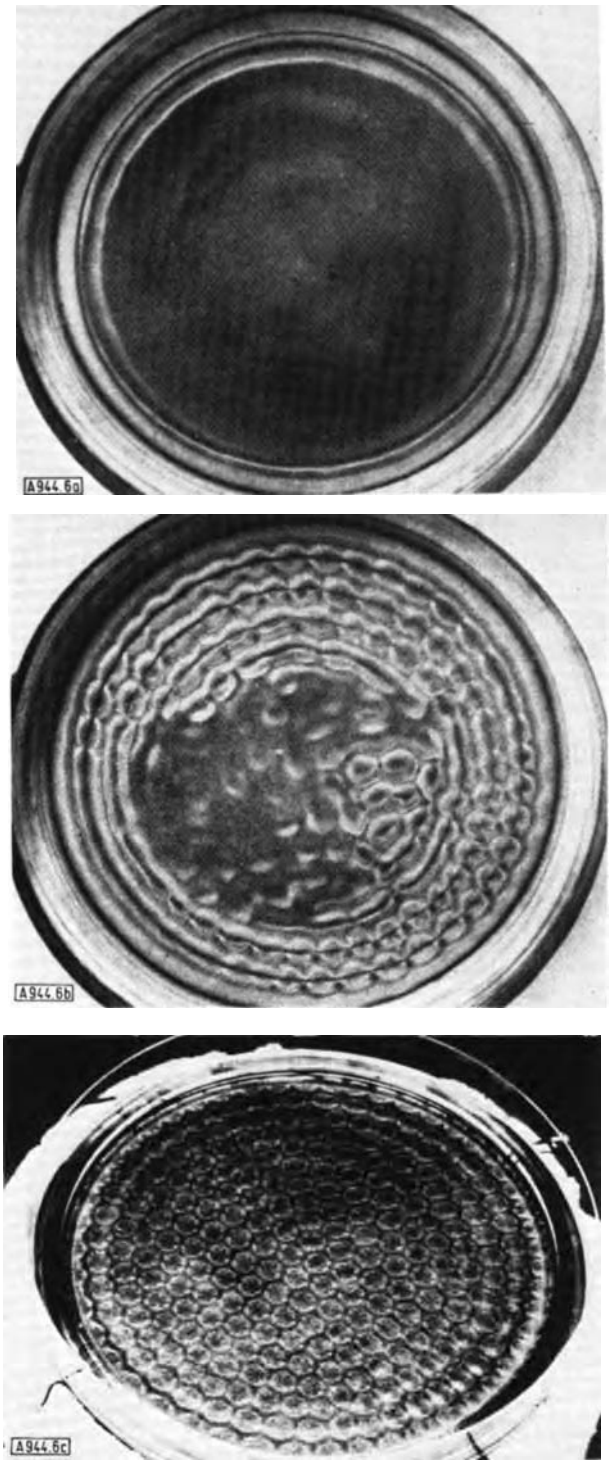

Fig. 6. Structure formation in a fluid heated from below. Diameter of vessel ≈20 cm. a) The beginning of heating with formation of circular structures. b) Continuation of heating and the beginning of cell formation. c) Further heating and formation of regular hexagonal cells.

Many astronomers and cosmologists now believe that stellar systems were formed on the same principle. A galaxy is an amorphous mass, which is subjected to cosmic flows. These flows might be the result of nuclear reactions and of convective flows determined by cosmic temperature gradients, or of atoms moving from high to low density centers. The sum of all these flows is considered to be responsible for structure in the galaxies.

Turing calculated that there would be a range of critical rates of reactions where structure was bound to appear if chemical flows, such as a chemical reaction involving diffusion through a tissue, were substituted for physical flows[47]. He called this phenomenon the chemical basis of morphogenesis. Chemical engineers working on catalytic gas cracking found to their dismay that *Turing*'s calculations were correct, and that at a certain rate of reaction structural forms appeared which deposited themselves on the walls of the cracking tubes, thus strongly impairing their catalytic properties.

Zhabotinskii[48,49] detected another type of structure formation, namely, a time dependent one. He observed that on oxidative decarboxylation of malonic acid with potassium bromate in the presence of cerium(III) sulfate, a colored intermediate was obtained whose concentration changed periodically. He postulated the following reactions:

$$Ce^{3+} \xrightarrow{BrO_3^-} Ce^{4+}$$

$$Ce^{4+} \xrightarrow{HOOC-CHBr-COOH} Ce^{3+} + Br^-$$

The latter reaction is of second order and the first one is autocatalytic. In the reaction with malonic acid, the initial concentration of Ce^{4+} decreases slowly with time due to the build-up of Ce^{3+}. As soon as enough Ce^{3+} accumulates, the mechanism becomes periodic. Thus *Zhabotinskii* obtained chemical reactions which produce chemical waves as a function of time; in other words, chemical reactions which appear and disappear in an oscillatory manner. Translated into biological processes, these reactions might well be the principle governing biological clocks. In the experiments on heterogeneous polymerization (Section 3.2) we had practically the same sort of phenomena. A wave of acid molecules emerges, it diffuses out, another wave appears, and so on. We might even—if we are very optimistic—translate the termination reaction into a fixation of the structure, like the poisoning of the catalyst which ensues according to *Turing*'s mechanism.

5. The Transition to Self-Reproduction

In Section 4 we dealt with dynamic structures resulting from flow interactions. The number of such dynamic structures is practically unlimited and their forms depend on the nature of the flows, their rates, the background against which they take place, *etc.* The transition from one such structure to another is not continuous but proceeds by discrete jumps based on all-or-none reactions, as do many biological transitions; those of the nervous system, for instance. It might be, and we make this postulate with the greatest reservations, that after the first macromolecules were created they formed a number of dynamic structures, due to the various flows around them, and some of these structures possessed catalytic activity. Such catalytic activity, after operation of various selection steps, could finally lead the molecule to a state that would bring about its self-reproduction.

6. Conclusion

While we might consider the formation of organic molecules out of the primordial broth as more or less proven,

all the other sequences of the formation of life still need much investigation in order to provide us with a comprehensive picture. However, as more data become available from year to year we may be justified in hoping that in the not too distant future at least some of the problems will be resolved.

What we can safely say now is that nature is controlled by the entirety of its laws, that these laws interact with each other, and that the scientific world emerges as a unity in which each particle has its own well defined place, time, and function.

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Molecular Hysteresis and Its Cybernetic Significance

By Eberhard Neumann[*]

The general foundations for a thermodynamic analysis of hysteresis phenomena in solutions and suspensions of polyelectrolyte systems are presented using examples of molecular hysteresis in biopolymers and membranes. The fundamental cybernetic significance of metastable states and molecular hysteresis for a physical interpretation of phenomena of life such as memory recording and biological rhythms is discussed.

1. Introduction

"*I believe that the ultimate goal of biological study is to 'translate' the phenomena of life into meaningful physical concepts*".—*Aharon Katchalsky*[**]

Modern physical chemistry of biological macromolecules has its roots in classical colloid chemistry. Because of their colloid properties high molecular weight constituents of biological cells and tissues have been called biocolloids. However, it was soon recognized that many cellular components thus classified were not colloidal aggregates of small molecules but large polymers of colloidal dimensions[1].

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The majority of biological macromolecules are linear polymer chains whose constituent monomer residues are electrically charged under physiological conditions of pH (about pH 7 to pH 8) and ionic strength (about 0.15 mol/l). Thus, for instance, all nucleic acids and acidic mucopolysaccharides are strong polyelectrolytes. The "surfaces" of many structural proteins, enzymes and biomembranes are densely covered with electrically charged groups and hence may be considered as polyelectrolyte systems.

In recent decades increased attention has been devoted to the electrochemical properties of biopolymers and biopolyelectrolyte organizations such as membranes. It has been recognized that various aspects of the specific organization and function of these cellular components are determined by the electrical interactions between them and their environment. Thus changes in structure and function of such systems may be regulated and controlled by electrical influences of the environment[2]. This cybernetic aspect gains particular interest in connection with another remarkable property of many "biocolloids": the capability of developing long-lived *metastable states.*

It is known from colloid chemistry that colloids of high electric charge may frequently exist in states that are not thermodynamically stable; such systems may undergo irreversible phase changes[3]. Thus it is not surprising that polyelectrolyte organizations of biopolymers and biomembranes are also capable of developing long-lived metastable states. In a variety of cases such metastabilities are reflected in pronounced hysteresis phenomena.

Perhaps the most familiar examples of long-lived metastabilities are the hysteresis loops displayed by ferromagnetic materials. But hysteresis phenomena are also seen in other fields of physics and chemistry; for instance, in melting-crystallization cycles of ammonium salts or in adsorption-desorption processes on porous materials. In these cases hysteretic behavior has been macroscopically interpreted in terms of domain and pore structures[4].

The term hysteresis was coined by *Ewing* in order to describe the (history-dependent) reaction of magnets to changes of the external electric field[5]. The word is derived from the Greek ὑστερεώ = to lag behind; for instance, in a magnetization-demagnetization cycle the magnetic polarization lags behind the applied magnetic field intensity.

In contrast to the classical macroscopic hysteresis phenomena in and on condensed phases, microscopic hysteresis of individual molecules in homogeneous solution has been discovered only recently. In 1956, *Cox*, *Jones*, *Marsh*, and *Peacocke* found that the potentiometric acid-base titration of ribosomal ribonucleic acid (rRNA) does not yield an equilibrium curve, but exhibits hysteresis in the degree of proton binding as a function of the pH value[6]. It was later shown that the rRNA hysteresis is an intramolecular phenomenon[7].

The result of a spectrophotometric acid-base titration of rRNA is shown in Figure 1. The hysteresis loop is practically time-independent (see Section 2) and can be traced several times. The direction of cycling, however, is fixed: titration of a neutral solution with acid always yields the lower branch, subsequent titration of the acidic solution with base always follows the upper branch of the limiting loop. Within the boundary loop we may obtain scanning

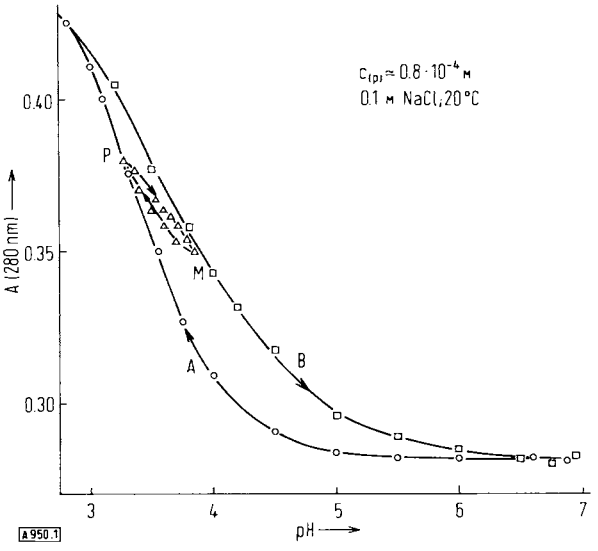

Fig. 1. Spectrophotometric titration of ribosomal RNA. Absorbance (A) at 280 nm as a function of pH; ○, acid titration (curve A); □, subsequent base titration (curve B); △, scanning loop. After [7].

curves similar to those observed in magnetic hysteresis. Because these inner curves reflect intermediary states of the system, scanning can in principle be used to scrutinize these states. The analysis of scanning curves is therefore a (novel) method of studying structural subunits in biopolymers such as rRNA in solution[8].

Numerous examples of hysteresis in solution and suspension are now known. Less numerous, however, are attempts to analyze these nonequilibrium phenomena and to elucidate the molecular origin of the underlying metastabilities. Indeed, for some time, hysteresis seems to have been considered by physicists and chemists as a curiosity that had to be avoided. That cycling of the loop is directional appears inconsistent with the time-independence of stable hysteresis loops. Directionality and changes with time are properties of irreversible (natural) processes whereas time-independence is the criterion for the limiting case of equilibrium (or of stationary states). Time-independent irreversibility, as reflected in long-lived hysteresis, apparently could not be treated either by the methods of classical thermostatics or by those of nonequilibrium thermodynamics.

It is the merit of *Aharon Katchalsky* to have contributed to a conceptual clarification of this apparent contradiction and, furthermore, to have recognized the important role which metastabilities and hysteresis may play in central phenomena of life, such as memory recording or biological rhythms[9,10]. Hysteresis is a well known expression of physical memory; thus modern computer technology utilizes hysteresis cycles of ferromagnetic and ferritic materials as memory devices for information storage.

In biology the mechanism of memory recording is still an unsolved problem. We may, however, conclude from biochemical and pharmacological studies that in the multistage process of biological memory formation there could plausibly be a physical step which is based on the directionality of hysteresis in macromolecules or membranes[11]. As a further dynamic aspect of hysteresis, circulation around a hysteresis loop presents in principle a possibility of producing periodicity on a molecular level by chemico-diffusional coupling[10,12]. This recognition is of great interest not only for the dynamics of enzyme catalysis

but also for the attempts to interpret biological rhythms[13] in terms of oscillatory chemical reactions.

Particularly challenging is the observation of hysteresis in nerve membranes[14, 15]. There is no doubt as to the fundamental role of electrochemical excitability of membranes for communication and control in all living organisms. However, the elementary processes of generation and conduction of bioelectric impulses are not well understood. It is remarkable that, according to *Adam*'s molecular theory of nerve excitability, the release of action potentials proceeds *via* short-lived metastable states of the nerve membrane[16].

These short remarks may indicate that the study of metastability and molecular hysteresis, as observed in macromolecules and membranes in solution and suspension, may be classed as an effort to "*translate*" some "*biological phenomena to physical-mechanistic concepts*"[9].

2. Thermodynamics of Hysteresis

2.1. Hysteresis and Metastability

In order to understand the special dynamic properties of hysteresis, we must delve into the nature of metastable states. Wherever long-lived hysteresis is observed, it indicates thermodynamically metastable states and cooperative nonequilibrium transitions. As is the case for macroscopic hysteresis phenomena in and on condensed phases, molecular hysteresis in solution and suspension also seems to be linked with domain structures. A domain may be defined as a structural unit or a structural region whose elementary units are able to change their state cooperatively, *i.e.* as a whole. Cooperative structural transitions in biopolymers and membranes may be thermodynamically classified as "diffuse" phase transitions and may be treated to a good approximation as first-order phase transitions[17–20].

It is frequently observed that phase changes encounter energy barriers which may hinder nucleation or/and propagation processes. These barriers must be reduced (*e.g.* by establishing nucleation centers) if the system is to pass through equilibrium states during the transition. If this is not possible under given experimental conditions, the system will pass instead into metastable states. Superheating and supercooling phenomena in thermal phase changes are manifestations of such transition barriers.

Thermodynamically the transition behavior of cooperative systems with metastabilities may be described by a state function $y(x)$ of the van der Waals type[21]. Figure 2a schematically shows such a function for the transformation of a domain between two states I and II. Between the two stable branches of this state function there is a (dotted) non-realizable range of instability. The equilibrium path, between B and D for I⇄II, may be traced at $x = x(G)$. If sufficiently high energy barriers prevent an equilibrium transition, changes in state can only occur *via* metastable regions. State I is metastable between B and 2 (region III), state II is metastable between D and 4 (region IV). The phase changes are unidirectional and irreversible, and take place at different x-values. At $x(I)$ the transition from I to II (between 2 and 3) occurs; the transition from II to I (between 4 and 1), however, occurs at $x(II)$. Thus, the irreversible phase changes fix a direction of cycling the hysteresis loop: 1→2→3→4→1.

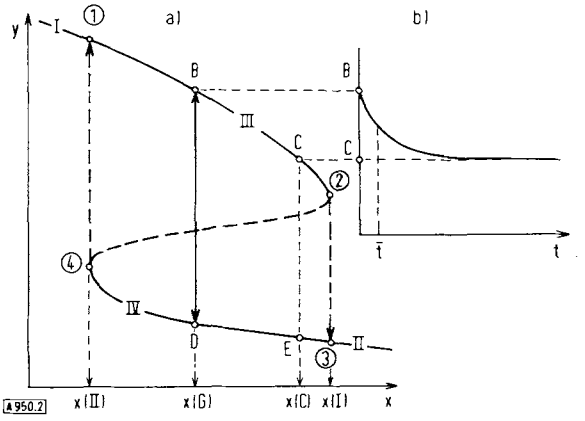

Fig. 2. a) Schematic representation of a phase transition: I, II stable states; III, IV, metastable states. y, internal parameter, *e.g.* volume or extent of reaction; x, external parameter, *e.g.* temperature or pH value. Cf. text. b) Time course $y(t)$ after a change from $x(G)$ to $x(C)$; see text.

In order to obtain hysteresis it is not necessary that both states I and II be metastable. It is sufficient that only one state develops metastability, *e.g.* state II in the region IV. In this case the transition IV to I would be irreversible whereas the change from I to II would occur along the equilibrium path at $x(G)$.

It may be seen from Figure 2 that in the hysteresis region between the transition points the internal parameter y is not a single-valued function of the external variable x. Thus, in contrast to equilibrium curves, hysteresis implies *two* values for y at *one* given value of x. Depending on the initial state, I or II, and depending on the direction of the change in x, the system may be either on the upper or on the lower branch of the $y(x)$ cycle. In the region of hysteresis the system "remembers" the history of tracing, the path by which the actual state change has been reached. It is this simple type of memory of path that distinguishes hysteresis from thermodynamic equilibrium. A state of equilibrium is "memoryless". Equilibrium may be reached by various routes; but once equilibrium is established, the system "forgets" preceding events. The memoryless state of equilibrium is the dead end of all directional, irreversible processes[9].

Abrupt, irreversible transitions characterize the dynamic behavior of a single domain. In an assembly of domains which have different stabilities, the distribution of transition points (along the x-axis) leads to an apparently smooth hysteresis curve, in which the consecutive irreversible transitions of individual domains cannot be distinguished (within experimental accuracy). Scanning curves may arise in systems having domains of different size and stability. Whereas hysteresis is a general indicator of cooperativity and metastability, scanning curves imply the existence of "polycrystallinity" or domain structures. Thus, the very observation of scanning curves classifies the rRNA molecule as such a "polycrystalline" multidomain system.

2.2. "Time-Independence" of Stable Hysteresis

As mentioned above, hysteresis is ascribed to thermodynamically metastable states[22], the lifetime of which may differ from one system to another.

Figures 2a and 2b illustrate how a hysteresis domain may react to a change of the environment. Suppose the system is in state I at point B and x is changed from x(G) to x(C). In typical examples one observes that the internal parameter, after an initial fast change (halftime $\bar{t}$), levels off to an apparently constant value C. If, within the limits of experimental accuracy, this value remains constant for long observation times $t \gg \bar{t}$, we attribute longevity to the underlying metastability. When the apparent temporal invariance holds only for short observation times, one speaks of short-lived metastable states. In the limit of an extremely small transition probability for the conversion from C to equilibrium at E, the extent of transition ξ remains apparently constant (*i.e.* $d\xi/dt = 0$) in spite of a non-zero affinity A. Hence the domain state C is comparable with a state of hindered equilibrium ($A > 0$; $d\xi/dt = 0$) such as the (metastable) mixture of H_2 and O_2 at room temperature, which reacts immeasurably slowly to give the thermodynamically stable H_2O vapor. It is a consequence of the apparent time-independence, that long-lived metastable states can be described by thermodynamic state functions, in the same way as equilibrium states.

The behavior of a domain is apparently reversible as long as external perturbations are restricted to the regions of metastability. If in our example the system at B is subjected to a displacement of x from x(G) to x(C) and then back to x(G), the domain will first change to point C and then will return from C to B. If, however, the external change proceeds beyond x(I), so that the irreversible transition to state II can occur, then—due to the directionality of the transition 2→3—the system remains in state II, even when the original condition of x(G) is reestablished. Only a change of x in the opposite direction, going beyond x(II), can bring the system back to its original condition in state I at point B. This nonequilibrium behavior means that such a domain may serve as a matrix for a permanent record of directed chemical or physical changes of the environment.

A cyclic variation of x, extending beyond both transition points x(I) and x(II), generally leads to hysteresis loops whose size depends on the cycling rate. Short-lived metastability results in relaxation hysteresis which, in the limit of very slow cycling, shrinks to the equilibrium curve. Stable hysteresis, however, does not decrease in size when the cycling velocity is diminishing (within the definition of time-independence for the underlying long-lived metastable states).

2.3. Entropy Production

The direction of rotation around a hysteresis loop is fixed by the entropy increase which accompanies directional (irreversible) changes of state. The entropy change dS of such a reaction system is correlated with changes in the internal energy dU, the work term dW and the chemical contribution $A d\xi$, through the Gibbs equation for chemical reactions (or phase changes) that proceed irreversibly at the (absolute) temperature T[23]:

$$T dS = dU + dW + A d\xi \tag{1}$$

In the equations defining the affinity and the variation of the advancement of reaction, respectively

$$A = -\sum_j \nu_j \mu_j; \quad d\xi = \nu_j dn_j \tag{2}$$

μ_j denotes the chemical potential, ν_j the stoichiometric coefficient, and n_j is the number of moles of component j (or of a component in phase j).

In nonequilibrium thermodynamics, the entropy change of a reaction system is divided into the two terms d_eS and d_iS[24]. Thus

$$dS = d_eS + d_iS \tag{3}$$

The term d_eS gives the contribution of the entropy which can be exchanged (as heat d_eQ) with the environment, $d_eS = d_eQ/T$, whereas d_iS represents the irreversible contribution created internally within the system. By definition d_iS is positive, $d_iS \geq 0$. If we now utilize the first law, $dU = d_eQ - dW$ and insert Eq. (3) into Eq. (1), we obtain

$$T d_iS = A \cdot d\xi \tag{4}$$

This relationship states that there is entropy production ($d_iS > 0$) in a reaction system only if the reaction or phase change proceeds irreversibly (*i.e.* if $A > 0$).

The entropy production accompanying a hysteresis cycle, Δ_iS, is derived by cyclic integration of Eq. (4):

$$\Delta_iS = \oint d_iS = \oint \frac{A}{T} d\xi \tag{5}$$

As noted earlier, the intrinsic directionality of hysteresis offers the possibility of recording "information" (and of erasing the record by continuing the cycle). This information (=negentropy) is based on entropy production of the recording matrix. The cost of storing as well as of erasing the imprint is "paid for" by investing work. That entropy production means loss of useful work can be derived directly from Eq. (1). For a closed cycle we have (at constant T)

$$T \oint dS = \oint dU + \oint dW + \oint A d\xi \tag{6}$$

Since the state variables S and U depend only on the state of the system, (for a variation which returns to the original state) the cyclic integrals $\oint dU$ and $\oint dS$ equal zero. Thus Eq. (6) reduces to

$$-\oint dW = \oint A d\xi \tag{7}$$

With Eq. (5) we obtain:

$$\Delta_i S = -\frac{1}{T}\oint dW \tag{8}$$

For $\Delta_i S > 0$, it follows that $\oint dW < 0$; *i.e.*, in order to close an irreversible cycle, work must be invested in the system.

2.3.1. Isothermal-Isobaric Hysteresis

The change in free energy dG accompanying a chemical reaction that proceeds irreversibly at constant temperature and at constant pressure p, is given by

$$(dG)_{p,T} = -A d\xi < 0 \tag{9}$$

We now denote the product $-T(\Delta_i S)_{p,T}$ as $(\Delta_i G)_{p,T}$, being the amount of free energy which is lost during an isothermal-isobaric hysteresis cycle.

$$(\Delta_i G)_{p,T} = -T(\Delta_i S)_{p,T} \tag{10}$$

This energy dissipation results from all processes k which occur irreversibly. Comparing Eq. (5) and Eq. (10) we may write:

$$(\Delta_i G)_{p,T} = -\sum_k \int_0^{\xi_k} A_k d\xi_k \tag{11}$$

In Eq. (11), ξ is normalized and, being the relative extent of reaction or degree of transition, varies between $\xi = 0$ and $\xi = 1$.

2.3.1. Calculation of $\Delta_i G$

Following the scheme of Figure 3, the calculation of $\Delta_i G$ may be performed in a general way. Using the symbols

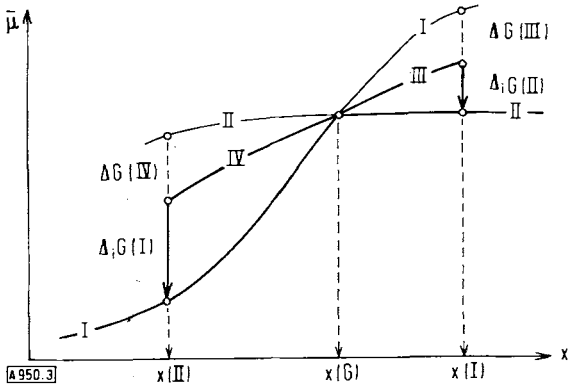

Fig. 3. Projection onto a μ-x plane of the mean chemical potentials μ̃, associated with the components or states. Cf. text and Fig. 2a.

given in Figure 2a we may choose the states I and II as reference states. The difference in free energy $\Delta G(\mathrm{II})$ between the states II and I at $x(\mathrm{II})$ is formally equal to the sum of the free energy changes $\Delta G(\mathrm{IV})$ accompanying the transition II→IV at $x(\mathrm{II})$ and the irreversible portion $\Delta_i G(\mathrm{I})$.

$$\Delta G(\mathrm{II}) = \Delta G(\mathrm{IV}) + \Delta_i G(\mathrm{I})$$

At $x(\mathrm{I})$ we have correspondingly:

$$\Delta G(\mathrm{I}) = \Delta G(\mathrm{III}) + \Delta_i G(\mathrm{II})$$

Since $\Delta_i G = \Delta_i G(\mathrm{I}) + \Delta_i G(\mathrm{II})$, the total dissipation of free energy during a hysteresis cycle is given by

$$\Delta_i G = \Delta G(\mathrm{II}) + \Delta G(\mathrm{I}) - \Delta G(\mathrm{IV}) - \Delta G(\mathrm{III}) \tag{12}$$

2.3.3. Thermal (Isobaric) Hysteresis

Provided that for thermal hysteresis the degree of transition ξ can be determined as a function of temperature, we derive from Eq. (5) a relationship for the measurement of the entropy production $(\Delta_i S)_p$.

$$(\Delta_i S)_p = \oint \left[\sum_k \frac{A_k}{T}\left(\frac{d\xi_k}{dT}\right)\right] dT \tag{13}$$

2.4. Energy Dissipation of Potentiometric Hysteresis

The hysteresis loops obtained in isothermal-isobaric potentiometric acid-base titrations are a direct measure of the energy dissipation and entropy production[25]. In a potentiometric hysteresis (cf., *e.g.*, Fig. 4) the mean degree of protonation $\bar{\alpha}$ corresponds to the internal parameter y and the pH value corresponds to x (in the notation of Fig. 2). The degree of protonation is defined as the ratio between the number of moles of bound protons and the number of moles of protonation partners.

The usual condition of such an acid-base titration is the retention of constant ionic strength during the titration cycle. This can be achieved by using a neutral salt whose concentration is large as compared to the concentrations of the reactants. If in addition the acid anion and salt anion are identical, *e.g.* are Cl^- ions, we may consider the chemical potential of the anions to be constant, and obtain, for instance, for the combination of HCl and NaCl: $d\mu_{HCl} = d\mu_{H^+} + d\mu_{Cl^-} \simeq d\mu_{H^+}$. Under this condition, the contribution of protonation to the change of the chemical potential of the (protonated) reactant j, is related (to a good approximation) to its degree of protonation α_j and the pH value by

$$\left(\frac{\partial \mu_j}{\partial \mathrm{pH}}\right)_{n \neq n_{HCl}} = -2.3\,RT\alpha_j \tag{14}$$

The notation $n \neq n_{HCl}$ means constant n except for n_{HCl} (cf.[8]).

The contribution of component j to the change of the free energy ΔG_k of the k-th protonation reaction in an acid-base cycle can be derived by cyclic integration of Eq. (14).

$$\Delta G_k = \oint \left(\frac{\partial \mu_j}{\partial \mathrm{pH}}\right)_k d\mathrm{pH} = -2.3\,RT \oint \alpha_{jk}\, d\mathrm{pH} \tag{15}$$

Since by definition

$$\Delta G_k = -\int_0^{\xi_k} A_k d\xi_k; \quad (\Delta_i G)_{p,T} = \sum_k \Delta G_k \tag{16}$$

we obtain from Eq. (11) and with $\alpha = \sum_j \sum_k \alpha_{jk}$ for the total dissipation of free energy

$$(\Delta_i G)_{p,T} = -2.3\,RT \oint \bar{\alpha}\,\mathrm{dpH} \tag{17}$$

The integral $\oint \bar{\alpha}\,\mathrm{dpH}$ is geometrically the area of the potentiometric hysteresis loop. Thus $(\Delta_i G)_{p,T}$ and the entropy production

$$\Delta_i S = 2.3\,T \oint \bar{\alpha}\,\mathrm{dpH} \tag{18}$$

can be experimentally determined.

Calculation of $\bar{\alpha}$. The number of bound protons is conveniently calculated from the difference in the amounts of acid or base which are necessary to bring the solution or suspension of the system to the same pH value as a "blank" solution. Since the investigation of hysteresis phenomena requires more than one acid-base cycle, more detailed relations (as usually needed) have to be used in order to calculate $\bar{\alpha}$. Such general equations have been given by *Revzin*, *Neumann*, and *Katchalsky*[7].

2.5. Protonation Energy of Polyelectrolyte Systems

In those regions of the hysteresis in which protonation is reversible or apparently reversible (as in the metastable regions), the formalism of protonation equilibrium may be applied. For polyelectrolyte systems, the pH dependence of the degree of protonation α_j of the group j is given by

$$\log \frac{1-\alpha_j}{\alpha_j} = \mathrm{pH} - \mathrm{p}K_j^0 - \Delta\mathrm{p}K_j \tag{19}$$

In Eq. (19), $\mathrm{p}K_j^0$ is the pK value of the single monomer residue and the polyelectrolyte contribution to the pK shift is defined by the relation

$$\Delta\mathrm{p}K_j = \frac{z_j \cdot e \cdot \psi_j}{2.3\,kT} \tag{20}$$

In Eq. (20), e is the (positive) elementary charge, k is the Boltzmann constant, ψ_j is the electrical potential at the site of protonation j, and z_j is the charge number (with sign) of the groups which give rise to ψ_j. The value of ψ_j depends on the geometry of the system, the mean degree of protonation and on the ionic strength of the medium.

The thermodynamic analysis of potentiometric hysteresis cycles often requires a knowledge of the free energy of protonation $\Delta_p G$. For the residue j, the standard value of this quantity is given by

$$\Delta_p G_j^0 = -2.3\,RT(\mathrm{p}K_j^0 + \Delta\mathrm{p}K_j) \tag{21}$$

Provided the pK value of the monomer residue is known, $\Delta_p G_j$ can be determined by calculating $\Delta\mathrm{p}K_j$ (cf. [26]).

2.6. Aim of Thermodynamic Hysteresis Analysis

The thermodynamic relations discussed in Section 2 provide the general framework for the analysis of hysteresis phenomena in chemical reactions or phase changes. The central task of such an analysis comprises the identification of those processes which occur irreversibly. For this purpose a comparison of measured and calculated values for $\Delta_i G$ may be useful.

Especially in polyelectrolyte systems, the thermodynamic analysis of temperature and ionic strength dependences may give hints as to the nature of the energy barrier which causes the metastable states and forces the system to hysteretically circumvent this barrier.

From a comparison of the Eqs. (8) and (10) we see that $(\Delta_i G)_{p,T}$ is a measure of the energy investment for an isothermal-isobaric hysteresis cycle. Therefore the thermodynamic analysis leads in principle to the determination of the free energies which must be invested in the system in order to re-establish the metastable states. The role of metastable states in triggering directed processes, at low expenditures of energy, is discussed in Sections 7 and 8.

3. Hysteresis in Nucleic Acids

3.1. Synthetic Polynucleotides

Especially pronounced hysteresis phenomena have been observed in potentiometric and spectrophotometric titrations of complexes composed of homogeneous synthetic nucleic acids. As a representative example, the result of a potentiometric acid-base titration of the polynucleotide complex poly(A)·2poly(U) is shown in Figure 4 (cf. [8]).

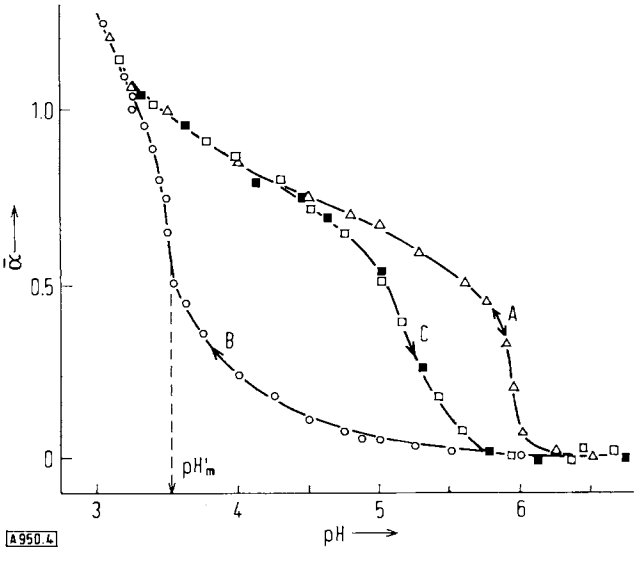

Fig. 4. Potentiometric titrations (degree of protonation $\bar{\alpha}$ as a function of pH) at 20 °C: a) 0.1 M NaCl solution of poly(A) and poly(U) mixed in the molar ratio of the polymers 1:2; ○: acid titration (curve B); □, subsequent base titration (curve C). b) 0.1 M NaCl solution of poly(A); △, (curve A). Polymer concentrations at pH 7: a) $c = 3.24 \times 10^{-4}$ M (A·2U); b) $c = 3.2 \times 10^{-4}$ M (A).

The three-stranded (A · 2 U) complex is formed when polyriboadenylate, poly(A), and polyribouridylate, poly(U), are mixed at neutral pH and sufficiently high ionic strength in the molar ratio of the polymers 1 : 2[27]. The double-stranded complex poly(A) · poly(U) may be obtained upon mixing the single strands in the molar ratio 1 : 1[28]. In these helical multistranded complexes the heterocyclic bases adenine and uracil are specifically associated by way of H-bonds and regularly stacked upon each other. Due to the cooperatively stabilized base stacking such systems may be considered as "unidimensional" crystals. (Because of their polyelectrolyte nature the stability of multistranded polynucleotide complexes is strongly dependent on the ionic strength of the medium.)

The first indications of metastable forms in the A-U system are seen in the results of *Warner* and *Breslow*: the (A · U) complex, apparently stable at pH 5.5 with respect to the single strands, is formed only to a small extent if the polymers are first separately brought to pH 5.5 and then mixed together[28]. Similar results were obtained by *Steiner* and *Beers*[29]. Later, *Cox* discovered that the size of the hysteresis loops observed in spectrophotometric titrations of (A · U) complexes are dependent on temperature[30]. Poly(A), too, shows dependence on previous history[29, 31]. The partially protonated double helix poly(A) · poly(A) that is formed at acidic pH values, has a tendency to aggregate with increasing proton concentration. At a given pH, the extent of this aggregation depends on the ionic strength. Furthermore, the actual state of the system is determined by the sequence in which the parameters pH and ionic strength are changed. The aggregation of poly(A) occurs relatively slowly at pH values which are not too low, so that this aggregation does not seriously disturb experimental studies on the acid-base hysteresis in the A-U-system. (Aggregation of larger extent can be checked by the measurement of sedimentation coefficients.)

3.1.1. The (A · 2 U) Model System

The first thermodynamic analysis of molecular hysteresis was performed by *Katchalsky*, *Oplatka*, and *Litan* using *Cox*'s results for the A-U system[25]. In contradistinction to the original interpretation, however, neither the (A · U) double helix nor the (A · A) complex can here develop long-lived metastability, but only the (A · 2 U) triple strand[8].

The hysteresis in the acid-base titration of the A-U system accompanies the "transcrystallization" reaction between the (A · 2 U) triple helix and the (A · A) double strand. The overall reaction may be written (in terms of the reactive chain residues or segments) as

$$2(\mathrm{A}\cdot 2\mathrm{U}) \underset{\curvearrowright}{\overset{\curvearrowleft}{\mathrm{H}^+}} (\mathrm{A}\cdot\mathrm{A}) + 4(\mathrm{U}) \qquad (22)$$

In the pH range 3 to 7, the measured quantity $\bar{\alpha}$ (as shown in Fig. 4) reflects protons bound to (A) residues. In the course of the acid titration the (A · 2 U) complex does not directly transform to the protonated (A · A) helix, but is first (partially) protonated. (This conclusion is supported by the similarity of the sedimentation coefficient distributions between pH 7 and pH 4.) Thus, the measured quantity $\bar{\alpha}$ is a sum of two contributions, one from protons bound to the (A · A) double helix (degree of protonation α_2) and the other from protons bound to the triple helix (degree of protonation α_3). If ξ denotes the extent of the conformational change described in Eq. (22), we obtain for each pH value:

$$\bar{\alpha} = \xi\alpha_2 + (1-\xi)\alpha_3 \qquad (23)$$

The value of α_2 can be measured independently by titration of poly(A), whereas α_3 may be calculated using a relation analogous to Eq. (19); see Eq. (35).

In a similar way UV-spectroscopic titration data can be used to determine the pH-dependence of ξ. Figure 5 shows

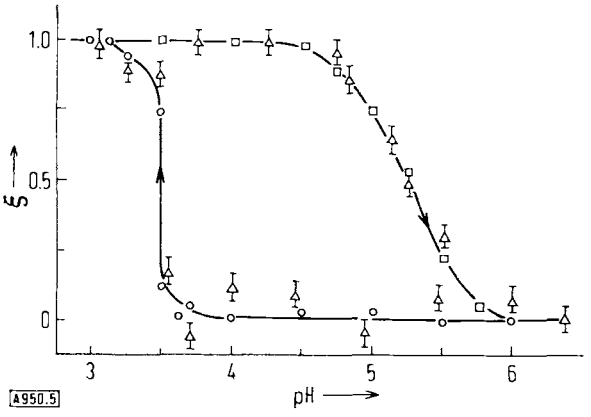

Fig. 5. Extent of reaction ξ as a function of pH. Experimental conditions as in Figure 4. ○, □: data of potentiometric and △: data of spectrophotometric titrations. Cf. [8].

that the same ξ(pH) is obtained irrespective of whether the quantity measured is $\bar{\alpha}$ or UV absorbance[8]. Furthermore, it is clearly seen that, along the acid branch, (A · A) formation occurs only at pH values near to pH 3.5. The transition on the acid branch is abrupt, whereas the smooth base branch points to an equilibrium transition.

a) Molar state variables. The measured (apparent) state variables of high molecular weight polynucleotides are independent of polymer concentration c_j[18, 32]. Therefore the polymer activity coefficients may be taken as constant and thus can be incorporated into the standard potentials μ_j^0. Thus

$$\Delta G = \sum_j \nu_j \mu_j = \sum_j \nu_j \mu_j^0 + RT \sum_j \nu_j \ln c_j \qquad (24)$$

For unit stoichiometric conversion, *i.e.* all $c_j = 1$ mol/l, it follows that

$$\Delta G^0 = \sum_j \nu_j \mu_j^0 \qquad (25)$$

and with Eq. (16) we obtain:

$$(\Delta_i G)^0 = \sum_k \left(\sum_j \nu_{jk} \mu_j^0 \right) \xi_k \qquad (26)$$

If we relate the state parameters to the number of moles of (A) chain segments, the measured $\bar{\alpha}$(pH) curve of Figure 4 directly yields the free energy loss, per mole of (A), for one isothermal-isobaric hysteresis cycle:

$$(\Delta_i G)^0_{p,T} = \sum_k \Delta G_k^0 \, \xi_k = -2.3\, RT \oint \bar{\alpha} \, \mathrm{d}\,\mathrm{pH} \qquad (27)$$

b) Calculations of $(\Delta_i G)^0$. As mentioned above there are indications that the base branch of the hysteresis in the A-U system is the equilibrium curve[8, 33]. Consequently our model system appears to have only *one* region of metastability. In this region the partial protonation of the triple helix represents a metastable pre-equilibrium. This equilibrium comprises the opening of (A·2U) segments

$$(A \cdot 2U) = (A) + 2(U) \qquad (28)$$

and the protonation of open (A) segments, according to $(A)+H^+=(AH^+)$.

The protonation equilibrium corresponds to state IV in Figure 2a. Thus, state II represents the (A·2U) triple helix, whereas state I represents the (A·A) double helix. If we now choose the chemical potentials of the separated single strands as reference, the calculation of $(\Delta_i G)^0$ becomes particularly simple. For our model system the general case as represented in Figure 3 is reduced to the scheme shown in Figure 6[8].

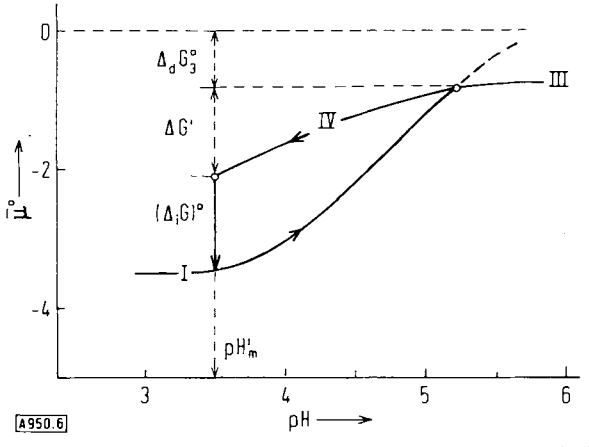

Fig. 6. Projection onto a potential-pH plane of the mean molar standard potentials $\bar{\mu}^0$ associated with the nucleotide segments; $\Delta G' = \alpha'_3 \cdot (\Delta_d G_3^0 + \Delta_p G_3^0)$, see Eq. (29).

By use of Eqs. (25) and (26) we can derive an expression for $(\Delta_i G)^0$ which corresponds to Eq. (12).

$$(\Delta_i G)^0 = \Delta_b G_2^0 + \Delta_d G_3^0 + \alpha'_3(\Delta_d G_3^0 + \Delta_p G_3^0) \qquad (29)$$

In Eq. (29), $\Delta_b G_2^0$ is the change in the free energy accompanying the reaction $(A)+H^+=\frac{1}{2}(AH^+ \cdot AH^+)$ at pH'_m (corresponding to x(II) in Fig. 3), $\Delta_d G_3^0$ is the free energy of the helix-coil transition (Eq. (28)), $\Delta_p G_3^0$ is the free energy change for the protonation of (A) segments in the triple helix (and may be calculated with Eq. (21)), and α'_3 is the extent of protonation at pH'_m.

It has been shown that, based on the assumptions underlying Eq. (29), the calculation and measurement of $(\Delta_i G)^0$ are in agreement[8]. Under the experimental conditions of Figure 4 we find that

$(\Delta_i G)^0_{p,T} = -1.4\ (\pm 0.1)$ kcal/mol (A)
$(\Delta_i S)^0_{p,T} = 4.9\ (\pm 0.1)$ cal/mol (A) deg

The agreement of the measured and the calculated $\Delta_i G$ value supports the interpretation of the hysteresis behavior, which was the basis of the calculation leading to Eq. (29). Accordingly, the hysteresis in our model system implies that a metastable protonation equilibrium exists as an intermediary during the acid titration.

It may be added that the energy loss in this hysteresis system is a rather small energy investment as compared to the average energy of stabilization of a chemical bond (≈ 50 kcal/mol).

3.1.2. (I·C) and (dC·dG) Complexes

It appears that three-stranded polyribonucleotide complexes (as opposed to double-stranded helices) tend to develop long-lived metastabilities. Polymer associates similar to the (A·2U) complex occur also in complexes of homopolymers of inosinic(I)-, cytidylic(C)-, and guanylic (G) acids. *Guschlbauer* and co-workers found that in the system poly(I)·poly(C) there are two hysteresis regions which are separated from each other by an equilibrium range[34]. A partially protonated triple strand of type (I·C·C) can be identified as an intermediate in the course of the (I·C) conversion[35]. (This is similar to the (A·2U) intermediate in the (A·U) conversion to (A·A) base pairs[8].)

Extended regions of metastability are observed in polydeoxyribonucleotides. Thus, the acid-base hysteresis in poly(dG)·poly(dC) covers about 6 pH units (between pH 2 and 8). This type of base pairing exhibits metastability in the physiologically relevant neutral pH range. Since it is known that rather long (dG·dC) stretches exist in DNA, we have here a possibility for a regulatory mechanism which could be specifically based on metastabilities in clustered (dC·dG) base pairs[34].

The energetics of such a mechanism could be estimated by a thermodynamic analysis of the hysteretic behavior of the (dG·dC) complex. In principle such an analysis can be performed in a similar way as in the (A·2U) system.

3.1.3. Thermal Hysteresis in Biopolymers

The UV-absorbance of some complexes composed of poly(dA) and polymers of substituted uridylic acids changes along a hysteresis loop during a heating-cooling cycle[36]. Similar thermal hysteresis has been observed in thio derivatives of the copolymer poly(dA-T) in solutions of high salt concentration (2 M NaCl)[37]. The hysteresis in this copolymer accompanies conformational changes between different helix types.

The capability of developing metastable states is apparently not restricted to complexes composed of several polyelectrolyte strands. For instance, the complex poly(A)·poly(1-vinyluracil) in which only poly(A) is an electrolyte, shows thermal hysteresis within a relatively broad temperature range[38].

There is a series of examples where hysteresis is due to unspecific aggregation and disaggregation of molecules. This category probably includes all the thermal hysteresis loops which have been found for a series of synthetic nucleic acids in water-methanol mixtures at lower temperatures[39].

Since optical parameters like UV absorbance at certain wavelengths are a measure of the degree of transition ξ of conformational changes, we may use Eq. (13) as a starting point for a thermodynamic description of thermal hysteresis in those biopolymers in which structural changes can be followed by optical methods.

3.2. rRNA Hysteresis

Long-lived metastabilities can be developed not only by long polynucleotides but also by shorter multistranded structured regions in nucleic acids. An example of such a system is the hysteresis of rRNA (cf., *e.g.*, [40]). Recent studies have shown that the rRNA hysteresis is clearly an intramolecular phenomenon[7]. The formation of metastable states in this biopolymer is linked with the presence of Mg^{2+} ions. Furthermore, the metastabilities occur only along the base branch of the boundary loop and along the scanning curves, whereas the acid branch represents the equilibrium curve. From the high thermal stability of the metastable forms and from the analysis of the UV spectrum as a function of pH, it was concluded that structured domains comprising mainly protonated G·G base pairs are the cause of the long-lived metastabilities in rRNA.

Questions concerning the possible role of metastable states in rRNA structures and in the regulation of ribosomal processes are the subject of further investigations[7].

4. Hysteresis in Proteins and Membranes

Hysteresis is also observed for structural changes in "globular" polyelectrolyte systems such as proteins, and lipoprotein and lipid vesicles. The hysteresis obtained in polyglutamic acid is considered representative for metastability in polypeptides. In this case the acid-base hysteresis has been interpreted in terms of specific aggregation-disaggregation processes[41].

For proteins, acid-base titrations are frequently used in order to determine type and number of buried groups[42]. However, the metastability indicated in the titration curves has rarely been thermodynamically analyzed. It should be stressed that the dissipation of free energy, $\Delta_i G$, of such systems represents a direct measure of the free energy stabilizing buried groups within the biopolymer.

An example of functional hysteresis in proteins has been discovered in the halophilic enzyme malate-dehydrogenase isolated from halobacteria of the Dead Sea[43]. The change of the catalytic activity of this enzyme with decreasing and increasing salt concentration follows a hysteresis loop (see Fig. 7).

Besides the hysteresis in nerve membranes[14, 15], metastabilities are also observed in suspensions of lipid vesicles. The thermal hysteresis found for such a spherical membrane system is bound to the presence of di- or trivalent ions or acetylcholine[20].

The acid-base titration of membrane fragments of the cell envelopes prepared from Dead Sea halobacteria yields a hysteretic proton binding curve (see Fig. 8). The size

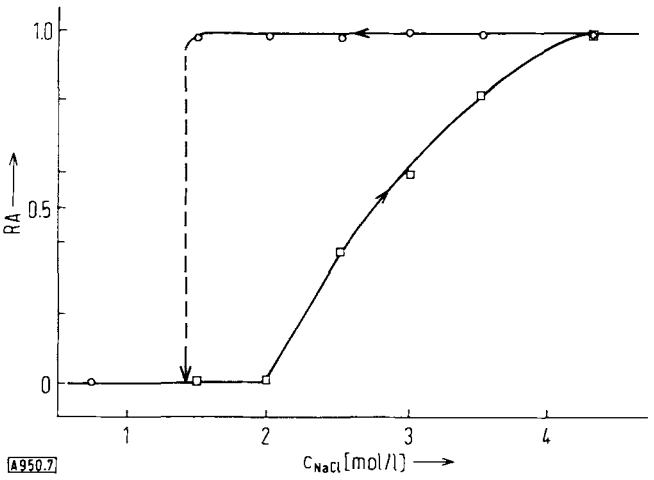

Fig. 7. Relative enzymatic activity, RA, of the haloenzyme malate-dehydrogenase at 30 °C; ○, values measured at decreasing and □, values measured at increasing NaCl concentration C_{NaCl} [43].

of this membrane hysteresis is dependent on the salt concentration; at a NaCl content smaller than 1 M, the hysteresis shrinks to give the equilibrium curve. If, at constant pH, the salt concentration is decreased and increased in a cyclic mode, one also obtains a hysteresis loop[44].

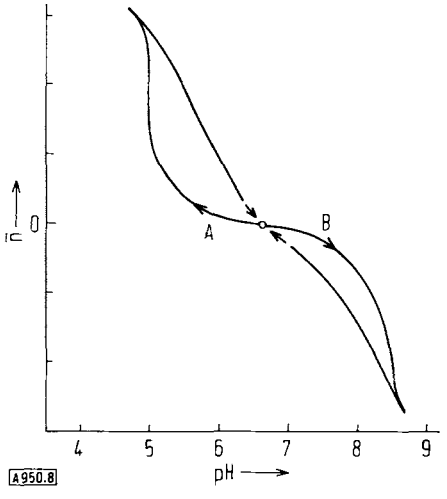

Fig. 8. Proton binding curve of suspended membrane fragments prepared from cell envelopes of Dead Sea halobacteria; $\bar{n}$, mean number of protons bound (in arbitrary units) as a function of pH. A, acid-base cycle in the acid pH range; B, base-acid cycle in the alkaline pH range; 20 °C, 3 M NaCl.

It is seen from Figure 8 that the nonequilibrium transitions indicated in the acid-base hysteresis occur in pH ranges which include the pK values associated with primary amino- and carboxyl groups of membrane proteins (at 3 M NaCl at about pH 8.5 and pH 5). The hysteresis in these membrane fragments is probably due to metastabilities in the "ion pairs" of electrostatically associated side groups. It appears that electrostatic interactions also contribute to the existence of hysteresis in the activity of our haloenzyme. In this protein, hysteresis derives from long-lived metastable states in the association-dissociation reaction between the dimer subunits of the tetrameric enzyme complex[43].

The cybernetic significance of hysteresis in membranes and catalytically active proteins will be discussed in Section 8.

5. Molecular Field Theory of Hysteresis

A general thermodynamic description of hysteresis cannot, of course, answer the question of the physical origin of this nonequilibrium phenomenon.

In the molecular hysteresis of nucleic acid complexes, long-lived metastability appears to be due to the cooperativity of base stacking and to the electrostatic interactions between the polyanions. Indeed, the first attempts at a molecular interpretation of the hysteresis in the A-U system include the assumption of an electrostatic nucleation barrier to the formation of protonated (A·A) sequences[25,8]. In this approach, however, only a qualitative interpretation has been given.

Recently, a molecular field theory of hysteresis has been developed[45]. According to this approach, a large energy barrier prevents opening of (A·2U) segments within the partially protonated triple helix. (The increased protonation in the acid titration compensates a part of the electrostatic repulsion energy arising from the phosphate residues of opposite strands, such that further opening of (A·2U) sequences is more difficult before a critical pH is reached.)

We may formally write the mean free energy $\bar{G}$ for the stabilization of an associate such as the (A·2U) segment as a sum of two terms:

$$\bar{G} = -\bar{A} + \bar{R} \tag{30}$$

The term $\bar{A}$ comprises all attraction contributions, primarily short range forces such as van der Waals- and hydrophobic interactions. The second term, $\bar{R}$, accounts exclusively for (long range) electrostatic *repulsion forces* between charged groups. We may further specify our "molecular field" model for the triple helix by defining the completely separated (non-interacting) single strands as a reference state for which $\bar{R}=0$. (Thus $\bar{R}$ is the relative mean free energy of the dissociated nucleotide residues in the triple helix.)

In our model the energy barrier for the separation of associated chain residues arises from the different manner in which $\bar{A}$ and $\bar{R}$ depend on the average distance, $\bar{d}$, between the opposite association partners. We may assume that $\bar{A}$ is zero for $\bar{d}>d_0$, where d_0 is the distance of maximum attraction. In the simple case of Coulomb repulsion, $\bar{R}$ is proportional to $1/\bar{d}$. Figure 9 schematically shows these correlations of $\bar{R}$ and $\bar{A}$ with $\bar{d}$.

Suppose now that the experimental conditions are such that only a few base residues within the cooperatively stabilized organization of the stacked (A·2U) triple helix could dissociate. The dissociated chain residues could not separate very far because their closed neighbors prevent them from moving apart from each other. A small distance between dissociated residues, however, means a high value of the $\bar{R}$ term. Thus dissociation of only a few associates would create an energetically unfavorable state, *i.e.* dissociation encounters a nucleation barrier.

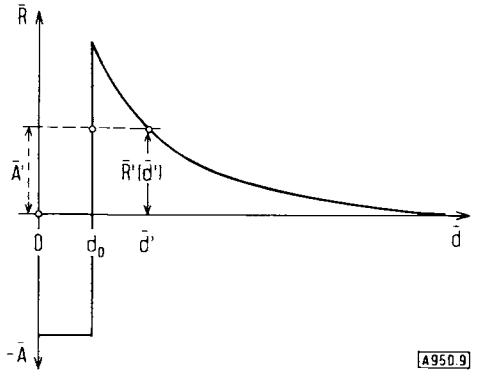

Fig. 9. Mean free energies $\bar{A}$ and $\bar{R}$ as a function of the mean distance $\bar{d}$ between the association partners in polyelectrolyte structures; see text.

This barrier can be decreased if $\bar{d}$ is increased. Such a decrease may be achieved by an increase in $\bar{A}$ (for instance, by a change in pH) thereby decreasing $\bar{R}(\bar{d})$. The thermodynamic condition for the onset of separation is given by

$$\bar{G}(\bar{d}) \geq 0.$$

If separation occurs at $\bar{d}=\bar{d}'$, we have at this point $\bar{A}'=\bar{R}(\bar{d}')$; see Fig. 9. Since now, however, $\bar{G}(\bar{d}')=\bar{A}'>0$, the dissociation of the entire assembly and the separation of the strands proceed irreversibly. All states for which $0<\bar{A}\leq\bar{A}'$ thus are metastable.

Since $\bar{R}$ depends on $\bar{d}$, it is obvious that $\bar{R}(d)$ is a function of the mean fraction, $\bar{f}$, of closed (A·2U) segments within a triple helix. We assume that this dependence is linear. Denoting the proportionality factor of this approximation by B, we may write

$$\bar{R} = B\cdot\bar{f} \tag{31}$$

It is easily seen that the term $\bar{R}$ has its maximum value if $\bar{f}=1$, while $\bar{R}=0$ for $\bar{f}=0$.

Since any chain segment in the triple helix is subject to the long-range electrostatic forces (or to the molecular field) of all segments, we may call Eq. (31) the molecular field approximation for our model.

In the range of experimental conditions, in which $\bar{G}$ depends on $\bar{d}$ and thereby on f, we may calculate the total free energy G_{tot} as a function of f by the following relation:

$$G_{tot} = -\bar{A}\cdot f + (1-f)\cdot B\cdot f + RT[f\ln f + (1-f)\ln(1-f)].$$

It can be shown that for $B>2RT$, the state function G_{tot} has two minimum values, one being associated with the metastable state and the other with the thermodynamic equilibrium state. Such an energy diagram containing two minima has already been used by *Borelius* in order to interpret long-lived metastability and hysteresis[22].

An important result of the theory is a condition for the existence of thermodynamically metastable states:

$$B > 2RT \tag{32}$$

For our (A·2U) model system, the inequality (32) holds for lower temperatures (<50 °C), whereas for the (A·U) double helix $B<2RT$. At the Curie temperatur T_c, we have $B=2RT_c$; that is, for $T \geq T_c$, the hysteresis disappears and one obtains only the equilibrium curve[8].

The hysteresis loops obtained in membranes and protein complexes of high surface charge densities may be molecularly interpreted with a molecular field approach in a manner similar to the polynucleotide systems.

6. Hysteresis as an Analytical Method

The extreme longevity of the metastabilities in some biopolymers and membrane structures permits the use of hysteresis as an analytical method for the investigation of distributions of structural subunits. As already mentioned, the occurrence of scanning curves implies domain structures. The analysis of these scanning curves can, in principle, reveal the distribution function of the domains and their characteristic transition points. Once this function is known, the scanning behavior can be predicted[46,47].

Such an analysis is based on the Preisach model[48] which underlies *Everett*'s domain theory. In the simple model of independent domains, the domain distribution function $\phi(x)$ can be determined in a relatively simple way from a limited number of scanning curves. This requires, however, that the mean extent ξ_i of the irreversible changes (*i.e.* the fraction of transformed domains) be measured as a function of the external parameter x. Let us attribute to each domain a lower transition point x_l and an upper one x_u (corresponding to x(II) and x(I) in Fig. 2). From the relationship

$$\phi(x) = -\frac{\partial^2 \xi}{\partial x_u \, \partial x_l} \tag{33}$$

the function $\phi(x)$ can be derived using experimental $\xi_i(x)$ values[46].

By assigning a lower and an upper x-limit for each scanning step we may describe scanning processes in a simple way. Thus, the paths by which a point of the hysteresis can be reached are represented by a domain complexion[46]. This function describes the path-dependent history of a domain system in a manner analogous to the after-effect function introduced in 1876 by *Boltzmann* for the description of elastic after-effects depending on the previous history of deformation[49]. Thus, *Everett*'s domain complexion is a type of memory function, and the domain distribution function describes the "memory capacity" of a multidomain system.

In order to check whether a system of independent domains is present, one may use a key theorem of *Everett*'s theory. For independent domains the areas of $\xi_i(x)$ scanning loops between the same x-limits have to be congruent. If the ξ_i values cannot be evaluated, we may use a modification of this theorem due to *Enderby*[47]. In this case the *measured* scanning loops (*e.g.*, $\bar{\alpha}$(pH) curves) between the same x_l- and x_u values are compared. In a system in which the state of a domain does not depend on the states of the other domains, the intercepts at the same x value between each scanning loop are equal.

If we utilize this theorem for the scanning loops in an (A·2U) system with a relatively broad molecular weight distribution, we obtain the picture represented in Figure 10. It is seen that the "loop intercepts" $\Delta\bar{\alpha}$(pH) are equal to within 10% accuracy. Thus the (A·2U) complexes apparently behave independently.

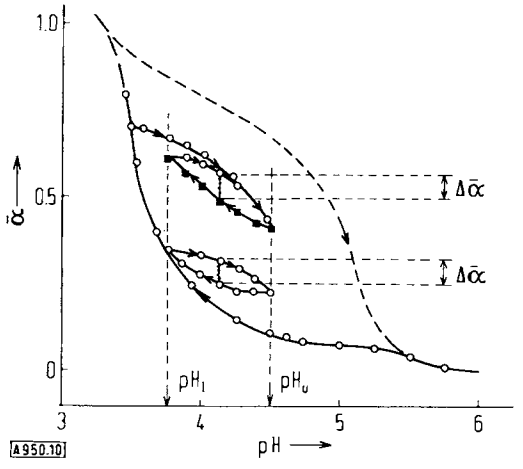

Fig. 10. Scanning loops in an (A·2U) system of broad molecular weight distribution; pH_l is the lower and pH_u is the upper pH limit of the loops. Comparison of the differences $\Delta\bar{\alpha}$ between the loops at the same pH value; cf. Figure 4 and see text.

Assuming that (A·2U) complexes of different molecular weight have different stabilities, the differentiation of the hysteresis boundary curve should yield the relative distribution of these stabilities and the relative amount of triple helices of different molecular weights along the pH scale. Thus, the analysis of the scanning behavior is in principle a method of determining the distribution of molecular weights in biopolymer mixtures.

7. Conformational Changes Induced by Electric Impulses in Polyelectrolyte Systems

Acid-base titrations are a standard technique for studying the thermodynamics of structural changes in ionizable systems. When the titrations are performed at different ionic strengths, it is possible to determine the electrostatic contributions to the energetics of structural changes. Such electrostatic contributions are particularly large in polyelectrolyte systems.

Eqs. (19) and (20) show that, for homogeneous polyelectrolyte systems:

$$\log\frac{1-\alpha}{\alpha} = \mathrm{pH} - \mathrm{p}K^0 - \frac{z\,e\,\psi}{2.3kT} \tag{34}$$

In this relationship we see that α may be changed by a variation in pH or by a change of the electrical potential

term ψ. In general, ψ is determined by the intramolecular field. This inner field may be influenced by the degree of ionization (protonation) and by the ionic strength of the medium, but also by external electric fields to which the system may be exposed.

In our hysteresis model system, the protonation pre-equilibrium of the (A·2U) complex in the pH-range above the irreversible transition at pH'_m may be described by the following relation:

$$\log\frac{1-\alpha_3}{\alpha_3} = pH - pK^0_{AMP} + \frac{e\psi}{2.3kT} + \frac{\Delta_d G_3}{2.3kT} \qquad (35)$$

In Eq. (35), pK^0_{AMP} is the pK value of adenosine monophosphate and $\Delta_d G_3$ corresponds to the pK shift due to the fraction of the (A) segments which dissociate from (A·2U) segments during protonation (cf. Eq. (28)). (ψ is negative, since it arises primarily from the negatively charged phosphate residues.) At $\alpha = \alpha'_3$ corresponding to $pH = pH'_m$, irreversible formation of (A·A) sequences occurs.

A change in ψ which leads to $\alpha > \alpha'_3$ may be achieved at constant pH by a change in the ionic strength. Indeed, the irreversible formation of the (A·A) double helix may be triggered by decreasing the salt concentration in a solution of metastable (A·2U) triple strands[33]. Recently, we have found that electric impulses (of an initial intensity of about 20 kV/cm and decaying exponentially with a relaxation time of about 10 μs) directly induce this conformational transition[50].

A polarization mechanism has been proposed to explain the electric induction of such conformational changes. In accordance with this idea, the external electric field shifts the ionic atmosphere of the polyelectrolytic (A·2U) complex and thereby induces a dipole moment. At the negative pole of the induced macro-dipole, the screening by the ion cloud of the negative phosphate residues is reduced. This, in turn, causes repulsion between the ends of the polyanions and leads finally to the unwinding of the triple helix[50].

A similar mechanism has been suggested to account for the induction of permeability changes in vesicular membranes of high surface charge density by electric impulses. Thus the displacement of the screening ionic atmosphere increases the mean distance between equally charged ionic groups on the membrane surface. The result is a permeability increase in the membrane. In this way we have interpreted the observation that electric impulses release biogenic amines from suspended chromaffin granules[51].

The electric impulses applied to solutions of the (A·2U) complex and to vesicle suspensions are comparable to the voltage pulses of the action potentials in nerve membranes. During excitation the electric field present across the nerve membrane changes in direction and intensity from about −70 kV/cm to about +50 kV/cm. We may assume that large electric fields act not only across the membrane but also in close proximity to it and (transiently) across the synaptic junction. Hence, any polyvalently charged system exposed to these fields could be affected in a similar way as the (A·2U) complex or the chromaffin granules.

Electrically induced conformational changes in macromolecules and membranes have been discussed as a possible mechanism for electrically controlled regulatory processes in general and for a recording of electric signals in particular. With this in mind we may consider directed structural transitions induced by electric impulses in metastable polyelectrolyte systems as *model reactions* for the process of imprinting nerve impulses in the neuronal structures involved in a possible physical record of memory.

It is known from physiological and biochemical studies that nerve stimulation accelerates the metabolism of innervated cells; nerve activity, for instance, enhances RNA and protein synthesis. The mechanism of coupling between electrical activity and chemical reaction is still unknown. In view of the hysteresis capacity of rRNA which might be electrically affected in a similar way as in the A-U system, the question is raised whether ribosomal activity may be regulated *via* rRNA metastabilities by the electrical activity of the cell.

Other cellular processes, too, are influenced by nerve activity. Thus the secretion of hormones and neuroeffectors (transmitter substances) is appreciably increased during nerve stimulation. The depolarization voltage which leads to increased hormone secretion in the chromaffin cell is comparable to the initial intensity of the voltage pulses which *in vitro* cause outflow of neuramines from the suspended chromaffin granules. It is therefore suggestive to assume a mechanism according to which nerve activity controls directly the intensity and the extent of neurosecretion by permeability changes in the membranes of the storage vesicles transiently attached to the nerve membrane.

Furthermore, it is suggested that the elementary processes of synaptic facilitation in the functional development of the central nervous system involve permeability changes combined with neuroeffector release induced by nerve impulses in membranes.

It is worth mentioning that a threshold value of the impulse intensity of about 18 kV/cm was observed for the release of conformational transitions in the (A·2U) model system as well as for the induction of permeability changes in the vesicle membrane. The threshold value of the depolarization voltage necessary to release action potentials in nerve membranes is about 20 mV; for an average membrane thickness of 100 Å, 20 mV correspond to a field intensity of 20 kV/cm. The similarity of these threshold voltages has revived the discussion on the chemical control of the ion flows underlying the action potentials. In line with this idea, conformational changes induced by impulses in membrane components are suggested as a mechanism for the activation of acetylcholine[53]. The relatively large amounts of heat accompanying the action potential imply the participation of chemical reactions in nerve activity. We note that chemical reactions and conformational changes which proceed irreversibly are accompanied by heat evolution due to dissipation of free energy. In this context it is of interest that during a depolarization-polarization cycle of the nerve membrane there is net heat production[53]. It is a moot question whether this heat is caused by membrane components which change their conformation along a hysteresis loop (cf. the hysteresis observed by *Tasaki* in squid axon membranes[14]).

8. Hysteresis as a Basis of Chemical Oscillations

The circular-vectorial property of hysteresis can be the basis for chemical oscillations. Microscopic chemical oscillations are of fundamental importance for a mechanistic interpretation of biological clocks[10,54].

The principle of molecular hysteresis-based periodicity is the coupling of a chemical reaction flux with a diffusional process. The condition for the development of oscillation in this case is hysteresis, either in the reaction flux or in the diffusional flux. For instance, a periodic change in the concentration of a reaction product will be caused by a substance which participates both in a chemical reaction catalyzed by a "hysteretic" enzyme, and in a diffusion process (which may be controlled by a membrane). (Theoretically, coupling between auto-catalysis and enzyme reaction can also lead to oscillations; cf., *e.g.*, [55].)

Periodic changes based on chemico-diffusional flow coupling have been known for a long time in the heterocatalysis of gas reactions on metal surfaces (see, *e.g.*,[56]). However, it has only recently been considered likely that such periodic processes may also occur on the level of single catalytically active molecules in homogeneous solution. In the halophilic malate-dehydrogenase we encounter an example of such a hysteretic catalyst[43].

Periodic changes in diffusional flows can be caused by membranes which change their permeability along a hysteresis loop. The cell envelopes of Dead Sea halobacteria could change their permeability as a function of salt concentration in this way, if the structural change indicated in the proton binding hysteresis could cause permeability changes in the cell membrane. The experimental results of *Ginzburg et al.*[57] indicate that the Dead Sea halobacteria periodically change their salt content. Further studies may elucidate whether there is a correlation between membrane hysteresis and the hysteretic activity of the enzymes, causing the "salt clock" of these organisms.

The principle of hysteretic chemico-diffusional coupling may be (qualitatively) described with the aid of an enzyme which becomes active by substrate binding at a critical substrate concentration S_2. The substrate S is assumed to flow at a constant rate in the reaction space; *i.e.*, the diffusional flow, J_d, of S is constant.

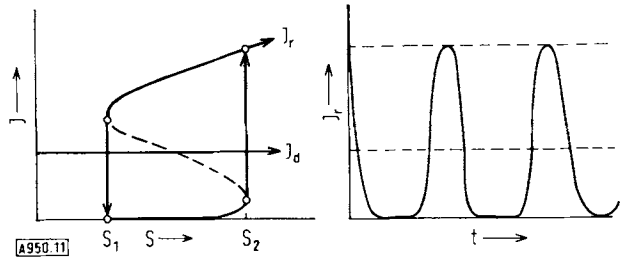

Fig. 11. Coupling scheme of transforming stationarity into periodicity by hysteretic chemico-diffusional coupling. S, substrate concentration; J_d, diffusional flux; J_r, reaction flux.

In the schematic representation of Fig. 11, it is seen that for $S > S_2$ the reaction flux $J_r(S)$ is larger than J_d. The breakdown of substrate is therefore faster than the influx of S. Thereby the substrate level in the reaction cell will sink until, at a critical concentration S_1, the enzyme becomes inactive. Now the reaction flux is smaller than the diffusional influx and substrate may accumulate until $S > S_2$. At S_2 the cycle can start again. The result is a periodic change of the reaction flux and therefore an oscillation in the product concentration[10].

In a similar way, a hysteretic permeability change in a membrane may transform a stationary flow into a periodic one. In this transducer function lies the fundamental significance of hysteretic macromolecules and membranes.

Whereas classical biology characterizes living organisms by stationary states (homeostasis), modern theories attempt to come closer to the actual dynamic behavior of biological organizations by a description which involves a quasi-stationary condition, with oscillations around a steady average[58]. Hysteresis represents a simple and energetically favorable mechanism for transducing stationarity into periodicity on a molecular level.

9. Closing Remarks

The discovery of conformational metastability in nucleic acids, proteins, and membranes has led to a new cybernetic approach to a dynamic interpretation of cellular behavior. It is worth noting that the dynamics of biological organization and function may be described by a general network theory recently developed by *Oster*, *Perelson*, and *Katchalsky*. In this approach, called network thermodynamics, "transducers" have been introduced as the coupling units between the network elements. It appears that macromolecules and membranes whose structure and function involve metastable states are particularly suited to act as elementary cybernetic units for "transducing" processes in general and for regulatory and memory reactions in particular. Metastable polyelectrolyte systems capable of storing "information" imprinted by ionic fluxes or electrical "activity" would be of significance for fast information processing with low energy expenditures.

In a dynamic picture of cellular organization and function there seems to be little room for perfect stability characterizing ideal equilibrium states. Even simple stationarity appears to be insufficient for a general description of central biological processes such as regulation and control of enzyme catalysis or membrane transport, information processing, or selforganization[60,61]. I believe that nonequilibrium approaches involving metastable states and molecular hysteresis may contribute to a better understanding of the complex dynamics of fundamental phenomena of life.

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The Cytochalasans: A New Class of Biologically Active Microbial Metabolites

By Michael Binder and Christoph Tamm[*]

A series of cytostatically active metabolites have been isolated from microorganisms in recent years. These compounds, which are chemically closely related, are of a new structural type. A highly substituted hydrogenated isoindolone unit is fused to an 11- to 14-membered macrocycle. The large ring may be carbocyclic or heterocyclic (lactone or carbonic diester). The absolute configurations of two cytochalasans (phomin and a cytochalasin D derivative) have been established by X-ray analysis. The biogenesis of phomin (cytochalasin B) is broadly known, and it is probable that all cytochalasans have a common biogenetic scheme. All the compounds of this class have a more or less pronounced specifically cytostatic action.

1. Introduction and Nomenclature

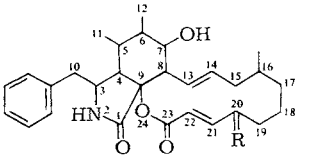
Under the title "The Cytochalasins as Research Tools in Cytology" *Carter*[1] recently published a review on the biological effects of a class of substances that has only been known since 1966, *i.e.* the cytochalasans. Ten members of this group have been isolated so far, and we felt it appropriate, as a complement to the above-mentioned article, to collect the chemical facts on the cytochalasans, elucidation of their structure, stereochemistry, and biogenesis in the form of this progress report. The biological properties of the cytochalasans are summarized in the last section. For detailed information, the reader is referred to the review cited.

All cytochalasans are metabolic products of microorganisms, and in some cases of molds. The isolation of these compounds resulted from the observation that culture filtrates of certain microorganisms have a cytostatic action on cell cultures *in vitro*[2].

The isolation of the first two substances of this class and the determination of their structure was achieved at about the same time, and independently of each other, in Basel[3] and by *Aldridge et al.*[4] in the research laboratories of ICI Ltd. in England.

The compounds isolated in Basel from culture filtrates of the microorganism *Phoma*, strain S 298, were named phomin *(2)* and dehydrophomin *(3)* from the name of the microorganism, while those obtained at ICI from cultures of *Helminthosporium dematioideum* were called cytochalasin A *(3)* and B *(2)*. This latter name refers to the biological activity of the two metabolites, and is derived from κύτος, meaning cell, and χάλασις, meaning relaxation. A direct comparison showed that phomin *(2)* is identical with cytochalasin B, and dehydrophomin *(3)* with cytochalasin A.

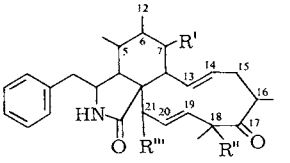
The British research group soon afterward reported the elucidation of the structures of two other cytochalasans, which had been isolated from cultures of *Metarrhizium anisopliae*[5]. These two compounds, which are chemically closely related to cytochalasins A *(3)* and B *(2)*, but belong to a different basic group of cytochalasans, were unfortunately also named cytochalasin C *(4)* and D *(5)* because of their biological action.



(1), $\Delta^{4,5}$; R = H, OH

(2), $\Delta^{6,12}$; R = H, OH

(3), $\Delta^{6,12}$; R = O



(4), $\Delta^{5,6}$; R' = R'' = OH; R''' = OAc

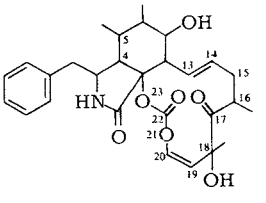
(5), $\Delta^{6,12}$; R' = R'' = OH; R''' = OAc

(6), $\Delta^{6,12}$; R' = R'' = R''' = OH

(7), $\Delta^{6,12}$; R' = OH; R'' = H; R''' = OAc

(8), $\Delta^{6,12}$; R' = R''' = OAc; R'' = OH

(9), $\Delta^{6,7}$; R' = H; R'' = OH; R''' = OAc



(10), $\Delta^{4,5}$

Precisely as in the case of phomin *(2)*, the structure of cytochalasin D *(5)* was also established on a second occasion, when *Minato et al.*[6] described a new antibiotic isolated from cultures of *Zygosporium masonii* in the research laboratories of Shionogi & Co. Ltd., Japan; these workers gave it the name zygosporin A *(5)*, after the microorganism. From data on zygosporin A *(5)* published before its structure was established, *Aldridge* and *Turner*[7] deduced that it was identical with cytochalasin D *(5)*; this was disputed

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Table 1. List of natural cytochalasans.

Cpd.	Trivial name	Systematic name	Microorganism	Ref.
		24-Oxa-[14]cytochalasans		
(1)	Cytochalasin F	(7*R*,16*R*,20*R*)-7,20-Dihydroxy-16-methyl-10-phenyl-24-oxa-[14]cytochalasa-4(5),13',21'-triene-1,23-dione	*Helminthosporium dematioideum*	[10]
(2)	*Phomin* = Cytochalasin B	(7*S*,16*R*,20*R*)-7,20-Dihydroxy-16-methyl-10-phenyl-24-oxa-[14]cytochalasa-6(12),13',21'-triene-1,23-dione	*Helminthosporium dematioideum*, *Phoma* spec. S. 298	[3, 4, 12, 14]
(3)	*Dehydrophomin* = Cytochalasin A	(7*S*,16*R*)-7-Hydroxy-16-methyl-10-phenyl-24-oxa-[14]cytochalasa-6(12),13',21'-triene-1,20,23-trione	*Helminthosporium dematioideum*, *Phoma* spec. S. 298	[3, 4, 12, 14]
		[11]Cytochalasans		
(4)	Cytochalasin C	(7*S*,16*S*,18*R*,21*R*)-21-Acetoxy-7,18-dihydroxy-16,18-dimethyl-10-phenyl-[11]cytochalasa-5(6),13',19'-triene-1,17-dione	*Metarrhizium anisopliae*	[5]
(5)	*Cytochalasin D* = Zygosporin A	(7*S*,16*S*,18*R*,21*R*)-21-Acetoxy-7,18-dihydroxy-16,18-dimethyl-10-phenyl-[11]cytochalasa-6(12),13',19'-triene-1,17-dione	*Metarrhizium anisopliae*, *Zygosporium masonii*	[5, 6, 8]
(6)	Zygosporin D	(7*S*,16*S*,18*R*,21*R*)-7,18,21-Trihydroxy-16,18-dimethyl-10-phenyl-[11]cytochalasa-6(12),13',19'-triene-1,17-dione	*Zygosporium masonii*	[9]
(7)	Zygosporin E	(7*S*,16*S*,18*R*)-21-Acetoxy-7-hydroxy-16,18-dimethyl-10-phenyl-[11]cytochalasa-6(12),13',19'-triene-1,17-dione	*Zygosporium masonii*	[9]
(8)	Zygosporin F	(7*S*,16*S*,18*R*,21*R*)-7,21-Diacetoxy-18-hydroxy-16,18-dimethyl-10-phenyl-[11]cytochalasa-6(12),13',19'-triene-1,17-dione	*Zygosporium masonii*	[9]
(9)	Zygosporin G	(16*S*,18*R*,21*R*)-21-Acetoxy-18-hydroxy-16,18-dimethyl-10-phenyl-[11]cytochalasa-6(7),13',19'-triene-1,17-dione	*Zygosporium masonii*	[9]
		21,23-Dioxa-[13]cytochalasan		
(10)	Cytochalasin E	7,18-Dihydroxy-16,18-dimethyl-10-phenyl-21,23-dioxa-[13]cytochalasa-4(5),13',19'-triene-1,17,22-trione	*Rosellinia necatrix*	[10]

at first by the Japanese workers, but was later confirmed by an independent elucidation of the structure[8].

A number of metabolites that were formed in small quantities, *i.e.* zygosporins D *(6)*, E *(7)*, F *(8)*, and G *(9)*, all of which are variants of cytochalasin D *(5)*, were also isolated from the fermentations of *Zygosporium masonii*[9].

In 1972, *Aldridge et al.*[10] published the structures of the last two cytochalasans known at that time. Cytochalasin F *(1)*, which is obtained from cultures of *Helminthosporium dematioideum*, is a double-bond isomer of phomin *(2)*. Cytochalasin E *(10)*, a metabolic product of *Rosellinia necatrix*, is the first member of the third group of cytochalasans.

The numbering of the basic skeletons of the cytochalasans differed as much as their names. To resolve the resulting total confusion, we recently suggested, together with the two other groups, a uniform systematic nomenclature for all cytochalasans[11], by which the three types and their derivatives can be easily designated as derivatives of a single basic type. The rules underlying the new nomenclature will now be briefly explained.

(I) The hydrogenated isoindole, including the macrocycle and carbon substituents on the isoindole except for the phenyl ring, is given the name cytochalasan. This name, which is derived from cytochalasin, seemed preferable to the corresponding name phoman derived from phomin (which should have received priority for historical reasons), since the name cytochalasin B is used in the majority of biologically oriented publications. (II) The size of the macrocycle is indicated by the number of ring members given in square brackets immediately in front of the name "cytochalasan". (III) The stereochemistry of the ring fusion sites is fixed. It is the same for all cytochalasans, and so need not be specially indicated. This is also largely true of the carbon substituents on the isoindole portion. (IV) Inserted hetero atoms, with the exception of the isoindole nitrogen, are indicated by the corresponding prefixes. Other features (further substituents, double bonds, absolute configuration) are indicated in accordance with the usual rules. The new system has the advantage that numbering differs only in those parts of the molecules that are chemically different.

The ten cytochalasans isolated so far are given in Table 1 with their trivial names, the systematic names, and the microorganisms from whose cultures they were isolated.

Because of the length of the systematic names, which are largely important only to specialists, the trivial names given in Table 1 are used whenever reference is made in the text to a specific cytochalasan. Where a cytochalasan has been given more than one trivial name, we shall use the chronologically earlier name, which is given in italics in the table, though no significance should be attached to this preference.

To facilitate comparisons between the various cytochalasans, only the new uniform numbering will be used. This numbering in accordance with[11] does not agree with that used in the existing publications[3-10,12-14,16-21], and so cannot be applied to these articles.

2. Elucidation of the Structures

2.1. Phomin *(2)*, Dehydrophomin *(3)*, and Cytochalasin F *(1)*

The reactions carried out by the two groups of workers in the determination of the structure of phomin *(2)* are

summarized in Figure 1. In both cases, the molecular weight and the molecular formula of phomin *(2)* were determined by mass spectrometry. The spectral data showed the presence of a five-membered lactam ring, an ester group, two hydroxyl groups, two *trans*-disubstituted olefinic double bonds, and an exocyclic methylene group. The base peak in the mass spectrum at *m/e* 91 is characteristic of a benzyl group (tropylium ion).

In the first case[3, 12], phomin was subjected to ozonolysis with reductive work-up ($NaBH_4$); the two γ-lactams *(11)* and *(12)* and the aliphatic triol *(14)* were isolated. The triol *(14)* reacted with periodate, and therefore contained a glycol grouping. From the mass spectrum and the NMR spectrum, it was deduced that this fragment was 6-methyloctane-1,2,8-triol *(14)*, and this was confirmed by degradation to (3*R*)-3-methylpimelic acid *(17)*. This substituted pimelic acid could also be synthesized from (+)-pulegone *(18)*, and was identical with the degradation product. Since the absolute configuration of the chiral center in (+)-pulegone *(18)* is known, this fixed the stereochemistry at C(16) in phomin *(2)*.

The structures of the two γ-lactams *(11)* and *(12)* were determined mainly by double resonance experiments. The lactam *(11)* reacted with periodate, and it followed that the hydroxyl group in the six-membered ring was situated α to the exocyclic methylene group.

Atoms 22 and 23 of phomin *(2)* are not present in *(12)* or in *(14)*. The postulated cleavage product, probably glycolic acid *(15)*, could not be detected.

In dehydrophomin *(3)*, one of the two hydroxyl groups of phomin *(2)* is replaced by a keto group. It was clear from the NMR spectra that the hydroxyl group in question was that situated on C(20). The ene-dione, *i.e.* the partial sequence C(20)—C(23), gives a characteristic absorption in the UV spectrum. Finally, dehydrophomin *(3)* could be prepared from phomin *(2)* by treatment with CrO_3/pyridine. Under the action of light, the compound isomerizes to 21-*cis*-dehydrophomin, which exists in equilibrium with the *trans* form.

The manner in which the partial structures fit together to give the formula *(2)* for phomin was again established on the basis of NMR data and irradiation experiments.

Very much more material was available in the second case[14], and it was therefore possible to use drastic degradation methods.

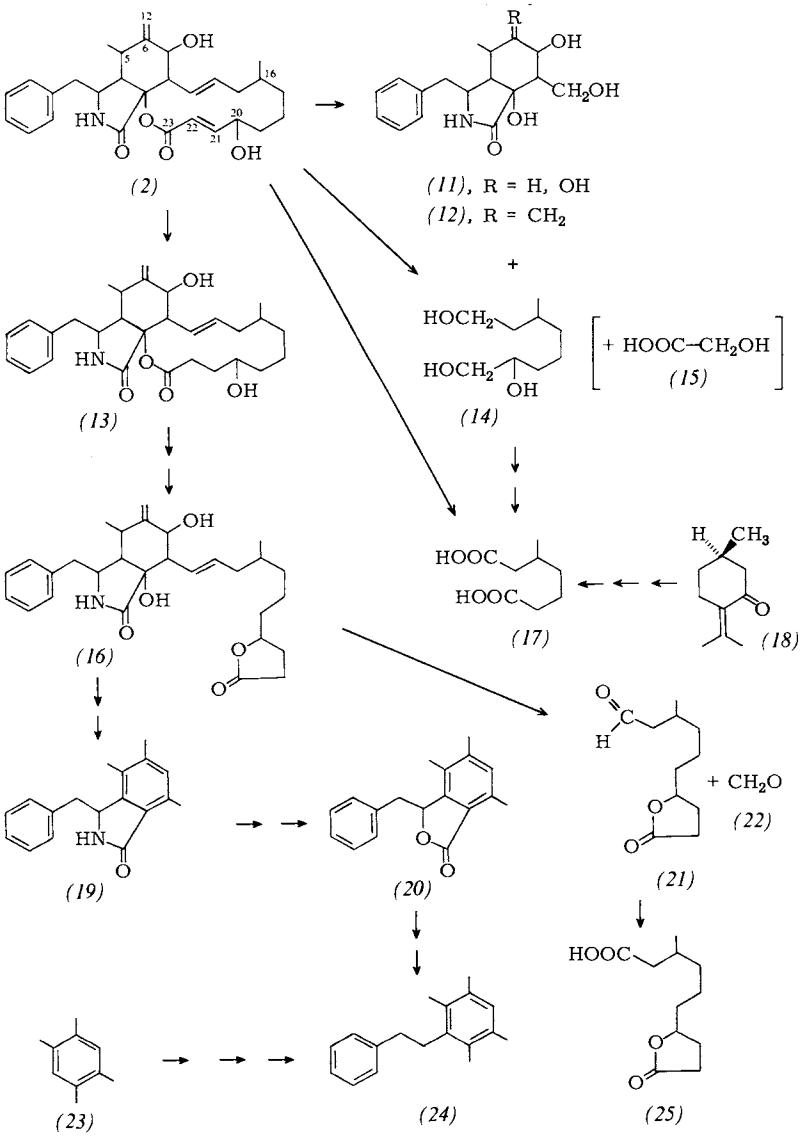


Fig. 1. Reaction sequences for the determination of the structure of phomin *(2)*.

Vigorous oxidation of phomin *(2)* with nitric acid again gave 3-methylpimelic acid together with other products. Reaction of phomin *(2)* with $NaBH_4$ led to the 21,22-dihydro derivative *(13)*, from which the hydroxy acid formed by cleavage of the macrocycle, or its lactone with the 20-hydroxyl group *(16)*, was obtained by hydrolysis. It was therefore concluded that one of the two *trans*-disubstituted double bonds must have been part of the large ring. The position of the other double bond was found by ozonolysis of the lactone *(16)*. On treatment of the ozonolysis mixture with H_2/Pd, it was possible to isolate two products, the aldehyde-lactone *(21)* and formaldehyde *(22)* (from C(12)), but no fragment corresponding to the lactams *(11)* or *(12)*. The structure of the aldehyde-lactone *(21)*, from which the carboxylic acid *(25)* was obtainable by oxidation was conclusively shown by mass and NMR spectra.

The structure of the lactam portion of phomin was established by alkali fusion of the lactone *(16)*. The resulting phthalimide derivative *(19)* was converted *via* the phthalide *(20)* in several steps into the penta-substituted benzene derivative *(24)*, whose structure was demonstrated by synthesis from 1,2,4,5-tetramethylbenzene *(23)*.

The correct arrangement of the partial structure was again established on the basis of NMR data.

Cytochalasin F *(1)*[10], according to the NMR spectrum, which contains the signal of a vinyl methyl group instead of the signal of the exocyclic methylene group, is a double-bond isomer of phomin *(2)*. From the simplification of the C(3) proton signal, it was concluded that the double bond is situated in the 4(5) position. Cytochalasin F *(1)* can be converted *via* the $\Delta^{5(6)}$ isomer into phomin *(2)* by treatment with acid. These isomerizations are irreversible.

2.2. Cytochalasin D *(5)*

As was mentioned earlier, two independent routes were followed in the determination of the structure of cytochalasin D *(5)*; the principal steps in these determinations are shown in Figure 2.

In one case[5], alkaline hydrolysis of cytochalasin D *(5)* led to the acid *(30)*, whose structure was established by comparison with the NMR spectra of phomin *(2)*. Apart from the missing hydroxyl group on C(9), this acid corresponds to the partial sequence of atoms 1—16 in phomin *(2)*. The evidence for the remainder of the molecule is indirect, since no other hydrolysis fragment was obtained. The missing sequence C(18)—C(21) was determined by comparison of the NMR spectra of the acid *(30)* and of the intact molecule of cytochalasin D *(5)*, as well as by double resonance experiments. On the basis of the NMR data and a further degradation experiment, it was possible to fit this partial structure into the structure *(5)*. The dodecahydro derivative of cytochalasin D *(5)* was converted with $NaBH_4$ into the 17-hydroxy product *(26)*, from which the keto-aldehyde *(28)* was obtained with periodate. The formation of this methyl ketone rules out the reverse arrangement of the sequence C(18)—C(21), since such a molecule would give a dialdehyde.

The determination of the structure of cytochalasin D *(5)*[8] was more difficult for the Japanese workers. They did not have the experience from the determination of the structure of phomin *(2)*, nor was a comparison with the spectra of the 24-oxa-[14]cytochalasans possible. As in the previous case, the molecular weight and the molecular formula were determined by mass spectrometry. Acetylations and deacetylations provided information on the position and character of the hydroxyl groups in cytochalasin D *(5)*. Reduction with $NaBH_4$ led to the 17-hydroxy derivative *(27)*, from which the keto-aldehyde *(29)*, the unsaturated analog of *(28)*, was obtained with periodate. The structure of the sequence C(18)—C(21) was deduced from the NMR spectra of *(29)*. Oxidation of cytochalasin D *(5)* led to the 7-oxo derivative, an α,β-unsaturated ketone, which showed that the 7-hydroxyl group is α to the exocyclic methylene group C(12) in *(5)*.

The alkaline hydrolysis of cytochalasin D *(5)*, was carried out under milder conditions here than in[14], and led to the thermodynamically controlled mixture of two acids *(30)* that were epimeric on C(9). One of the two acids (the stereochemistry on C(9) was not discussed) was converted into the methyl ester and acetylated on the C(7) hydroxyl group. Ozonolysis of the resulting compound *(33)* gave two aldehydes. According to the NMR data for their semicarbazones, one of these aldehydes is methyl 3-formyl-2-methylpropionate *(32)*, while the other has the structure *(31)*. It was possible to hydrogenate the exocyclic methylene group selectively in the ester *(33)*. The resulting dihydro derivative *(35)* was converted into the diol *(34)* with osmium tetroxide, and cleavage with periodate then gave the aldehydes *(32)* and *(36)*. The structure of the aldehyde *(32)* was already known. Reduction of the aldehyde *(36)* with $NaBH_4$ gave two products, the diol *(37)* and the allyl alcohol *(38)* resulting from the elimination of water. When heated at 300 °C over Pd/C, both *(37)* and *(38)* gave the two aromatic derivatives *(39)* and *(40)*, which were identical with authentic preparations (from *Aldridge et al.*[14]).

2.3. Cytochalasin C *(4)* and Zygosporins D *(6)*, E *(7)*, F *(8)*, and G *(9)*

Cytochalasin C *(4)*[14] is a double-bond isomer of cytochalasin D *(5)*. In the NMR spectrum, the signals of two vinyl methyl groups replace the signal of the exocyclic methylene group and the doublet of the C(11) protons; it can therefore be concluded that the double bond is situated in the 5(6) position. This assumption is supported by the identity of the hydrogenated derivatives of cytochalasins C *(4)* and D *(5)*. Isomerization of cytochalasin C *(4)* to cytochalasin D *(5)*, corresponding to that carried out for cytochalasin F *(1)*, could not be achieved.

Zygosporin D *(6)* is 21-deacetylcytochalasin D, as was readily shown by deacetylation of cytochalasin D *(5)*.

Zygosporin E *(7)* is 18-deoxycytochalasin D. This was shown by treatment of the 7-*O*-acetyl derivative of cytochalasin D *(5)* with $SOCl_2$ in pyridine. The 18-chloro derivative was dehalogenated with zinc in glacial acetic acid. The product was identical with 7-acetylzygosporin E.

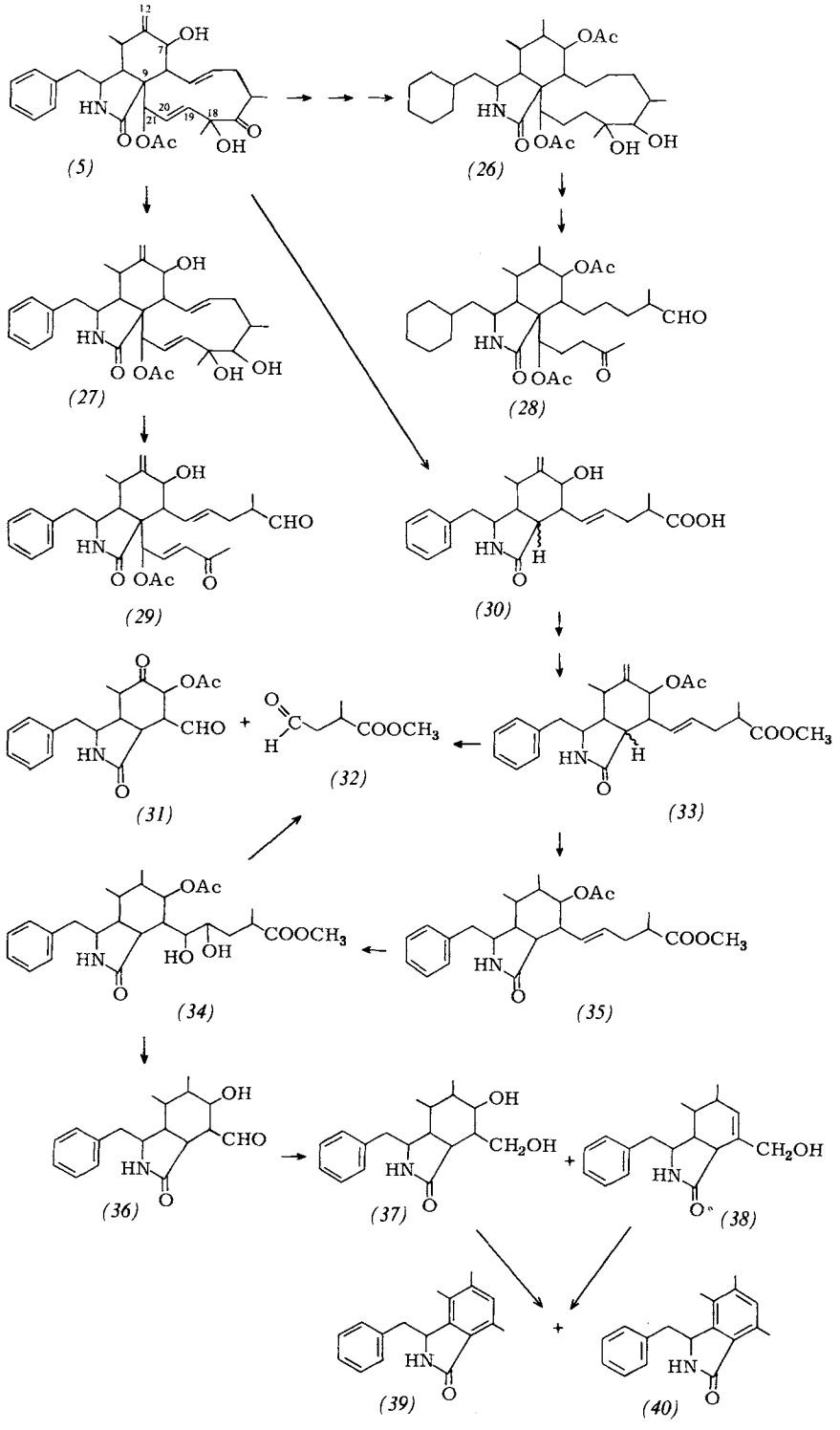


Fig. 2. Reaction sequences for the determination of the structure of cytochalasin D *(5)*.

Zygosporin F *(8)* is 7-*O*-acetylcytochalasin D.

The NMR spectrum of zygosporin G *(9)* contains the signal of a vinyl methyl group, two methyl doublets (C(11) and C(16)-methyl), and a methyl singlet (C(18)). The signal of the exocyclic methylene group has disappeared, as has that of the hydroxyl group on C(7). It follows that zygosporin G *(9)* is 7-deoxy-$\Delta^{6,7}$-cytochalasin D. Proof of this was provided by oxidation of cytochalasin D *(5)* to the 7-oxo derivative and reduction of the latter with ethanedithiol and Raney nickel to zygosporin G *(9)* and 6,7-dihydrozygosporin G.

2.4. Cytochalasin E *(10)*

A comparison of the NMR spectra of cytochalasin E *(10)* and cytochalasin F *(1)* shows that the partial structures are identical up to C(16). The $C_6H_6O_5$ unit that is missing according to the molecular formula found by mass spectrometry is shown by NMR data to contain a tertiary methyl group, a tertiary hydroxyl group, and a *cis*-disubstituted double bond[10]. The IR spectrum shows the presence of a carbonyl group and of a vinyl carbonate residue. Reduction of the 19(20) double bond gives the

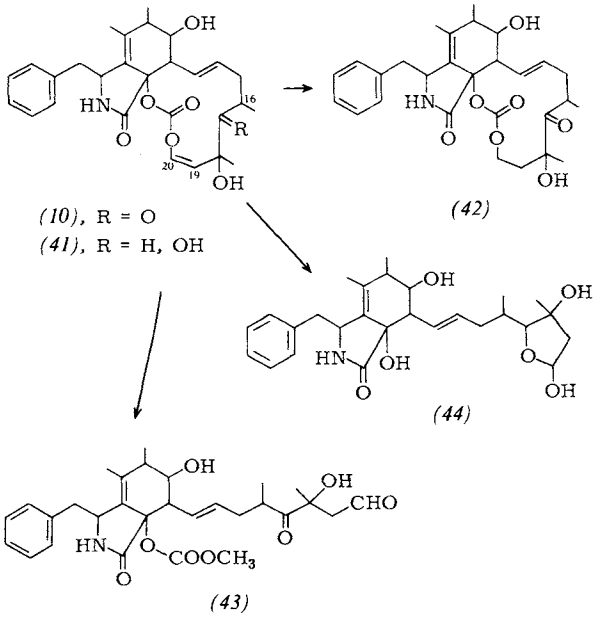


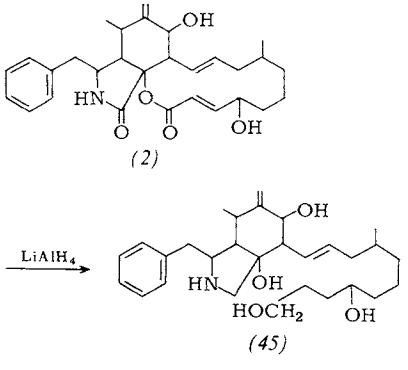
Fig. 3. Reactions of cytochalasin E *(10)*.

saturated carbonic diester *(42)*. Alkaline hydrolysis of cytochalasin E *(10)* leads to the aldehyde *(43)*; treatment of *(10)* with $LiAlH_4$ yields the alcohol *(41)* and the lactol *(44)*. The structure *(10)* for cytochalasin E agrees with these data. The reactions are summarized in Figure 3.

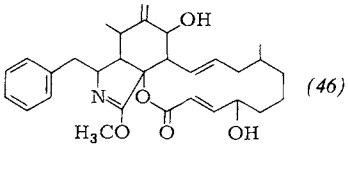
3. Other Reactions of Cytochalasans, Particularly of Phomin *(2)*

In this section we shall present a brief survey of some other reactions of the cytochalasans that were not mentioned in connection with the elucidation of their structures.

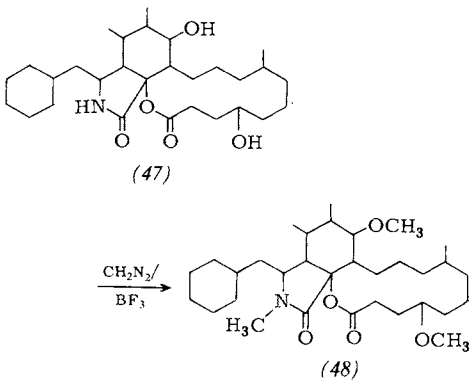
On treatment with $LiAlH_4$, phomin *(2)* first gives the known lactone *(16)*, while with a large excess of reagent and a longer reaction time, the amine *(45)* is obtained[12].



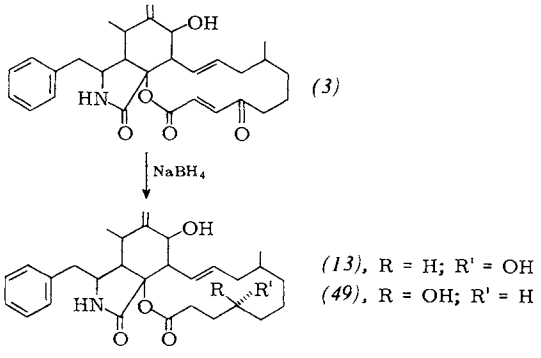
The attempted methylation of the hydroxyl groups of phomin *(2)* with Ag_2O/CH_3I in dimethylformamide yielded the phominimino methyl ether *(46)*[15].



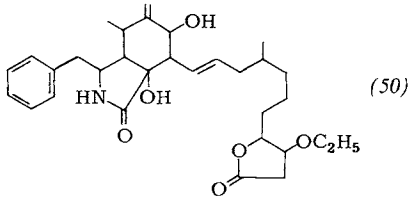
The dodecahydro derivative *(47)* of phomin *(2)* was converted with diazomethane/BF_3 into *N*-methyldi-*O*-methyldodecahydrophomin *(48)*[15].



The C(20) epimer *(49)* of dihydrophomin *(13)* was obtained together with *(13)* on treatment of dehydrophomin *(3)* with $NaBH_4$[15].



The hydrolysis of phomin *(2)* with aqueous-ethanolic alkali is accompanied by addition to the 21(22) double bond to give the product *(50)*[14].



Depending on the catalyst, phomin *(2)* can be hydrogenated to hexahydrophomin (only the olefinic double bonds are reduced) or to dodecahydrophomin *(47)*. Analogous reactions are also found for the other cytochalasans.

4. Stereochemistry of the Cytochalasans

Phomin *(2)* and cytochalasin E *(10)* each contain eight chiral carbon atoms, and cytochalasin D *(5)* contains nine; six of these are situated in the hydrogenated isoindole unit, and two or three in the macrocycle. Thus if one considers only the six chirality centers in the isoindole unit, there are 32 possible pairs of diastereoisomers, with four conformations for each of these pairs, since the six-membered ring may have the chair, boat, inverse chair, and inverse boat conformations. This gives a total of 128

possible steric arrangements. If the two or three centers of asymmetry in the macrocycle are also taken into account, this figure is multiplied by a factor of four or of eight.

The NMR data for phomin *(2)* allowed a first approximation to the solution of the problem[3, 12].

By appropriate quantitative application (with the necessary care) of the relation found by *Karplus* between the dihedral angle and the NMR coupling constant for vicinal protons[16] to the γ-lactam *(12)* obtained in the elucidation of the structure of phomin *(2)*, it was possible to reduce the 32 pairs of diastereoisomers to four, and three of the four conceivable conformations were also ruled out. The remaining four possible configurations, which are shown in Figure 4, could not be distinguished on the basis of the NMR spectra alone.

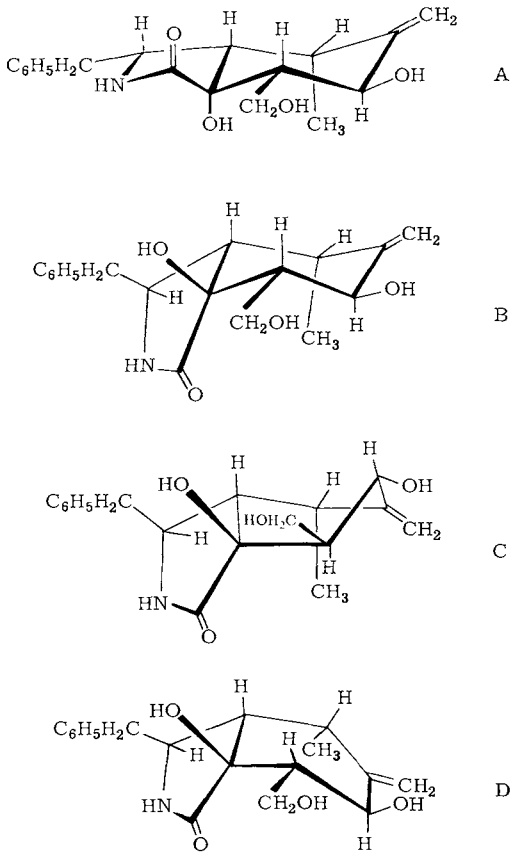


Fig. 4. Possible configurations of the γ-lactam *(12)*.

The absolute configuration at C(16) in phomin *(2)* was known by the correlation of the degradation product 3-methylpimelic acid *(17)* with (+)-pulegone *(18)*.

Similar considerations for cytochalasin C *(4)* gave two configurations for the partial structure in question; these corresponded to possibilities B and D in the case of phomin *(2)*[5].

The only possibility for the solution of the stereochemistry problem appeared to be offered by X-ray analysis, and it was therefore necessary to prepare suitable crystalline derivatives of the cytochalasans containing heavy atoms.

The first derivative of this type was the 18-*p*-bromobenzoic ester of 7-acetyl-21-deacetylcytochalasin D *(51)*[17] (cf. Figure 6) but the X-ray analysis of this compound gave only the relative configuration of cytochalasin D *(5)*; as

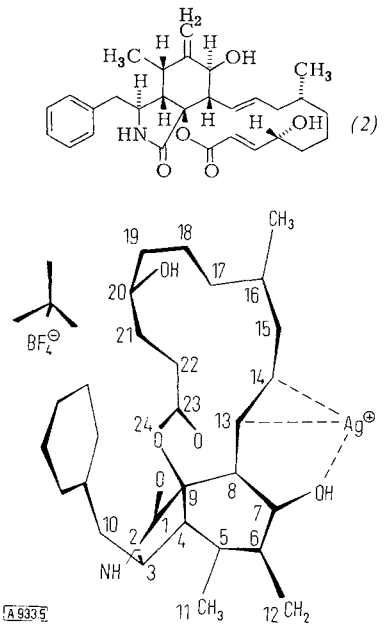


Fig. 5. Structure of the $AgBF_4$ complex of phomin *(2)* and absolute configuration of phomin *(2)*.

was later found, this was the mirror image of the actual configuration.

The second derivative was the silver tetrafluoroborate complex of phomin *(2)*[18]. From the known stereochemistry on C(16), it was possible in this case to give the absolute configuration of phomin *(2)* directly. The steric structure of the complex and the stereochemistry of phomin *(2)* are shown in Figure 5.

The assignment of the absolute configuration based on correlation with (+)-pulegone was also confirmed independently by the calculations. The stereochemistry found in this way corresponds to possibility D in Figure 4; this shows the correctness of the spectroscopic considerations.

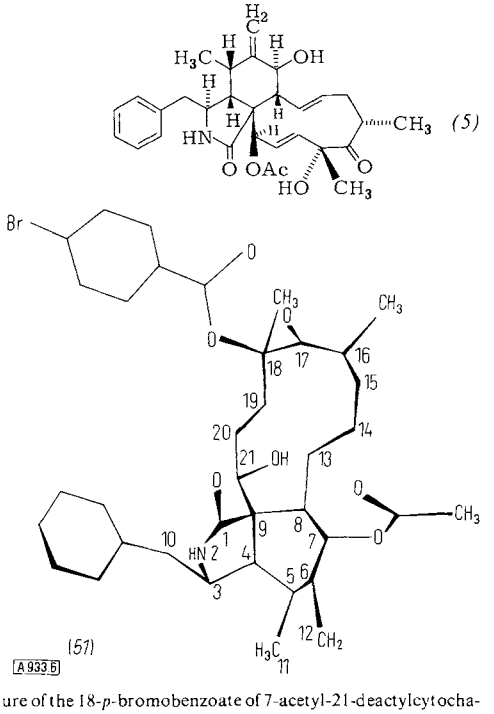


Fig. 6. Structure of the 18-*p*-bromobenzoate of 7-acetyl-21-deactylcytochalasin D *(51)* and absolute configuration of cytochalasin D *(5)*.

Detailed calculations[191] finally also led to the correct absolute configuration for the cytochalasin D derivative *(51)*. The steric structure of the derivative *(51)* and the stereochemistry of cytochalasin D *(5)* are shown in Figure 6.

The fusion of the five-membered and the six-membered rings of the isoindole part of the molecule is *cis* in both cases. The six-membered ring is in a flexible boat form. This allows two conformations for the bicyclic system, which differ only slightly and probably have very similar energies; one of these conformations is found in the crystal of the $AgBF_4$ adduct of phomin *(2)*, and the other in the derivative *(51)* of cytochalasin D *(5)*. The NMR spectra of some phomin derivatives suggest that these two conformers can readily change into one another in solution.

The stereochemistry of cytochalasin F *(1)* is probably the same as that of phomin *(2)*; nothing can be said about the configuration of the additional center of asymmetry C(6).

The configuration of the isoindole part of the molecule is probably also the same in cytochalasin E *(10)* as in cytochalasin F *(1)* and phomin *(2)*. The stereochemistry on C atoms 16 and 18 is not yet known; it could correspond to that in cytochalasin D *(5)*.

As is shown by the structural determinations, the stereochemistry of cytochalasin C *(4)*, and of zygosporins D *(6)*, E *(7)*, F *(8)*, and G *(9)* is identical with that of cytochalasin D *(5)*. The only exception is C(18) in zygosporin E *(7)*, whose configuration has not been determined. The configuration of this center of chirality cannot be deduced from the reaction sequence in which cytochalasin D *(5)* was converted into zygosporin E *(7)*.

5. Biogenesis of the Cytochalasans

Biosynthetic studies as carried out nowadays are typical "*in-vitro*" experiments. The general technique of isolation of the microorganism, cultivation on synthetic media, and incubation with special biogenetic precursors (usually radioactively labeled or labeled with isotopes) hardly corresponds to the conditions enjoyed by the organism in nature. Further problems are presented by the instant of incubation with the precursor, the form in which it is supplied, and the ability of the cell to absorb it. The optimization of such problems is difficult, and it is surprising that very good results are obtained even under conditions that could be quite unrealistic. It should be noted, however, that the result of a biosynthetic investigation must always be carefully formulated, *e. g.* as follows: Under

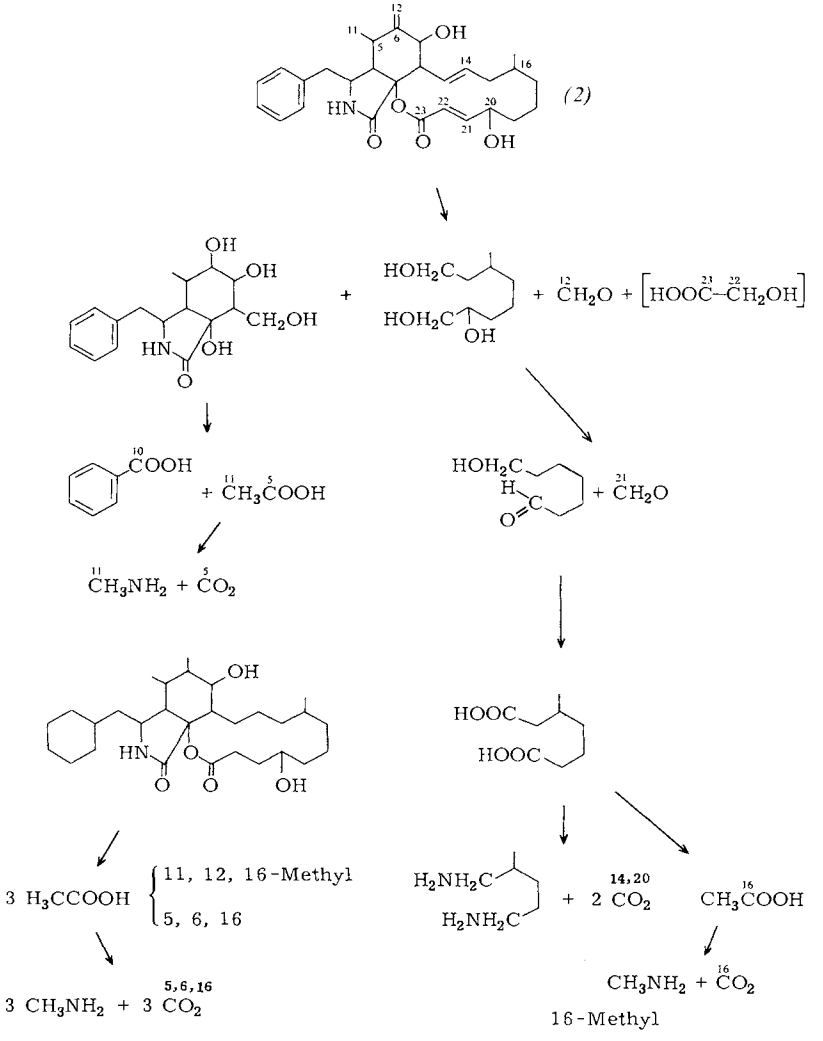


Fig. 7. Degradation reactions of phomin *(2)* for the localization of the radioactive C atoms.

the particular conditions used by us, the organism X can synthesize the molecule Y from the precursor Z, though this does not necessarily mean that it does so in nature.

Experimental data on the biogenesis of cytochalasans are available at present only for phomin *(2)*[20]. Investigations with cytochalasin D *(5)*[21] are in progress.

The procedure was as follows. The supposed, radioactively labeled precursors[*] were each added to nutrient solutions for the microorganism *Phoma* S 298, and the solutions were sterilized, inoculated with a suspension of the fungus spores, and incubated for 12 days. The cultures were then "harvested", and the phomin *(2)* present in the culture broth was isolated. The precursors used were selected on the basis of a working hypothesis on the possible biogenetic synthesis of phomin *(2)*, which was ultimately confirmed. The precursors, their radioactivity and the percentage incorporation into the phomin preparations are shown in Table 2.

Table 2. Data on the precursors and percentages (absolute) incorporated into the phomin preparations.

Precursor	Activity [mCi]	Incorporation in phomin (absolute) [%]
[1-^{14}C]-DL-phenylalanine	0.1	4.9
[2-^{14}C]-DL-phenylalanine	0.1	6.7
[U^{14}C]-L-phenylalanine	0.1	10.4
[4'-T]-L-phenylalanine	1.0	10.4
[1-^{14}C] Na propionate	0.1	0.29
[2-^{14}C] Na propionate	0.1	0.4
[1-^{14}C] Na malonate	0.1	0.33
[2-^{14}C] Na malonate	0.1	1.04
[1-^{14}C] Na acetate	1.0	0.123
[methyl-^{14}C]-L-methionine	0.1	1.96
[2-^{14}C]-mevalonate	0.25	0.007

To localize the radioactive atoms incorporated into the molecule, phomin *(2)* was subjected to specific chemical degradation; the reaction schemes are indicated in Figure 7.

The degradation first involved reactions that had been carried out in the determination of the structure of phomin *(2)*[3, 12], and was then confined to methods, such as cleavage with periodate, Kuhn-Roth oxidation, and Schmidt degradation of acids, that proceed specifically in high yields. The small quantity of radioactive material and the small quantities incorporated were limiting factors. The atoms in phomin *(2)* that were detected by the degradation are indicated in Figure 8.

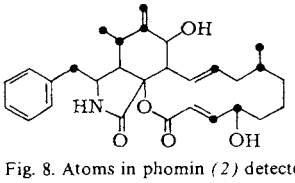


Fig. 8. Atoms in phomin *(2)* detected by the degradation.

The results obtained in this way will not be described individually, but are summarized in Figure 9.

Phomin *(2)* is thus synthesized biogenetically from one molecule of phenylalanine (including the carboxyl group),

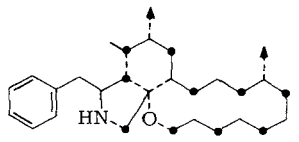


Fig. 9. Basic structural units for the biogenesis of phomin *(2)* (for explanation see text).

nine acetate units or one acetate unit and eight malonate units, and two C_1 residues from methionine. A nonaketide[*] is probably first formed from the acetate or malonate units, and this, attached by an amide linkage to phenylalanine, could then be fitted together to form a carbocyclic precursor of phomin *(2)*. The lactone ring of phomin *(2)* would be formed only later from the large carbocyclic ring by insertion of an oxygen atom after the fashion of a Bayer-Villiger oxidation.

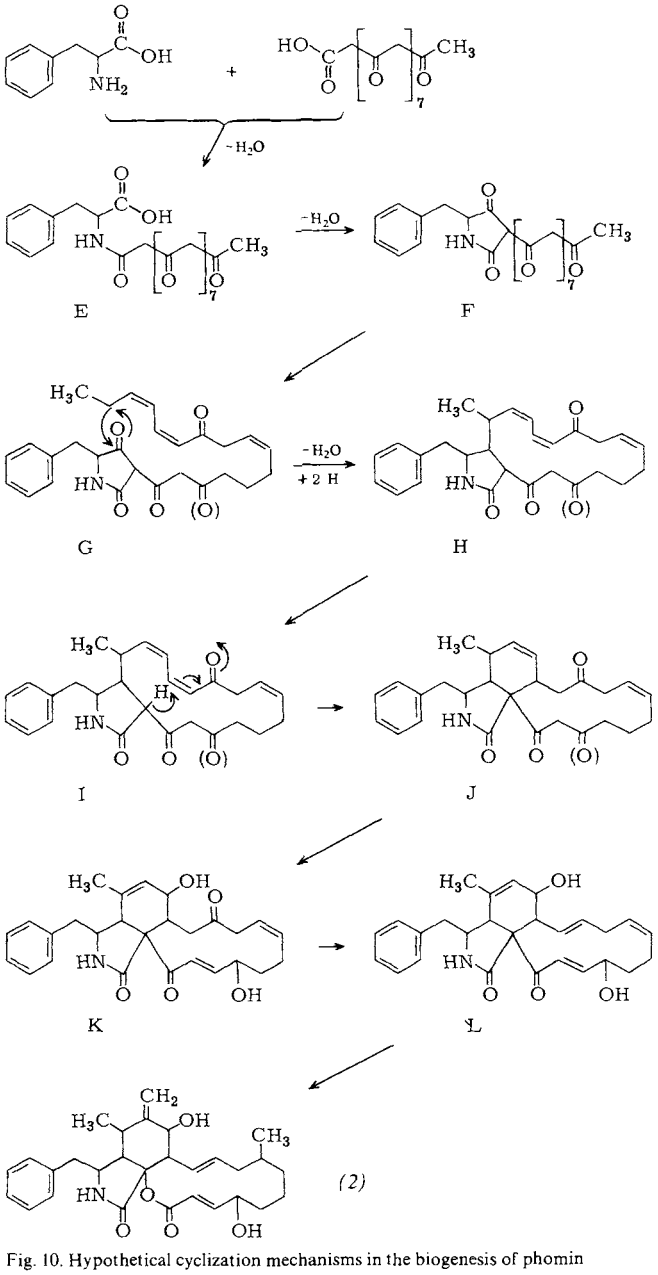


Fig. 10. Hypothetical cyclization mechanisms in the biogenesis of phomin *(2)*.

[*] Since only small quantities of the precursor were incorporated in some cases, it was not possible to use [^{13}C]-labeled compounds.

[*] The term "ketide" is applied here to compounds having β-keto groups.

It is known that instead of the hypothetical polyketide, a saturated or unsaturated fatty acid would also be a possible direct precursor of a secondary metabolite derived from acetate[22]. Experiments with Na [1-^{14}C]-linolenate and Na [16-^{14}C]-palmitate (as an equivalent of an octaketide) gave negative results in this respect[23]. The degradation showed that the low activity incorporated was distributed homogeneously over the molecule. It is thus probable that the acetogenin part of phomin *(2)* is derived from a higher oxidation state, *i.e.* the polyketide or a biogenetic equivalent, rather than from the largely reduced form, *i.e.* the fatty acid. We can only guess at present about intermediates and cyclization mechanisms in the biogenesis of phomin *(2)*.

A scheme of this nature is shown in Figure 10. The individual steps, some of which are interchangeable in their order, all correspond to known reactions.

As was mentioned above, the amide linkage of the nonaketide to phenylalanine may be regarded as the initial step. The subsequent condensation of E leads to the five-membered ring of the lactam F, one of whose carbonyl groups reacts with the penultimate C atom of the ketide after reduction to G with formation of the 4,5 bond. Partial reductions and water eliminations yield the intermediate H, in which, after allylic oxidation on C(14) to form I, the bond C(8)—C(9) is formed by condensation (J). The rearrangement of the double bond from the 6(7) position into the 5(6) position and a further allylic oxidation on C(7) and (after reduction and elimination of water) on C(20) lead to the intermediate K, from which phomin *(2)* is formed *via* L by further reduction with elimination of water, two methylations on C(6) and C(16), *e.g.* with *S*-adenosylmethionine, and an oxygen insertion after the manner of a Bayer-Villiger oxidation. It need hardly be mentioned that all these steps are hypothetical.

The experiments with cytochalasin D *(5)*[21] have so far shown that the same precursors have been incorporated to a similar degree as in phomin *(2)*.

The great structural similarity of the three basic types of cytochalasan, *i.e.* the 24-oxa-[14]cytochalasans, [11]cytochalasans, and 21,23-dioxa-[13]cytochalasans enables us to postulate a common biogenetic scheme for all cytochalasans, which is shown in Figure 11.

The fundamental units of the biogenesis of the cytochalasans are the primary metabolites phenylalanine and a nonaketide or octaketide or their biogenetic equivalents. Phenylalanine is formed from shikimic acid, and is thus derived ultimately from sugars; the nonaketide or octaketide is formed from acetate units by a process similar to the synthesis of fatty acids, but without the reduction steps.

The linkage of phenylalanine to the nonaketide leads by path I to the 24-oxa-[14]cytochalasans, while linkage to the octaketide leads by path II to the [11]cytochalasans and to the 21,23-dioxa-[13]cytochalasans. The sequence of the next few steps has already been discussed. At some point (arbitrarily taken as different here from that in Figure 10), the oxidative insertion of oxygen atoms could occur in path I and path IIb, with formation of the lactone group on the one hand and the carbonic diester group on the other.

After the further steps mentioned, this would lead us to the structures that are finally isolated, *i.e.* the end products of the secondary-metabolic reaction sequences.

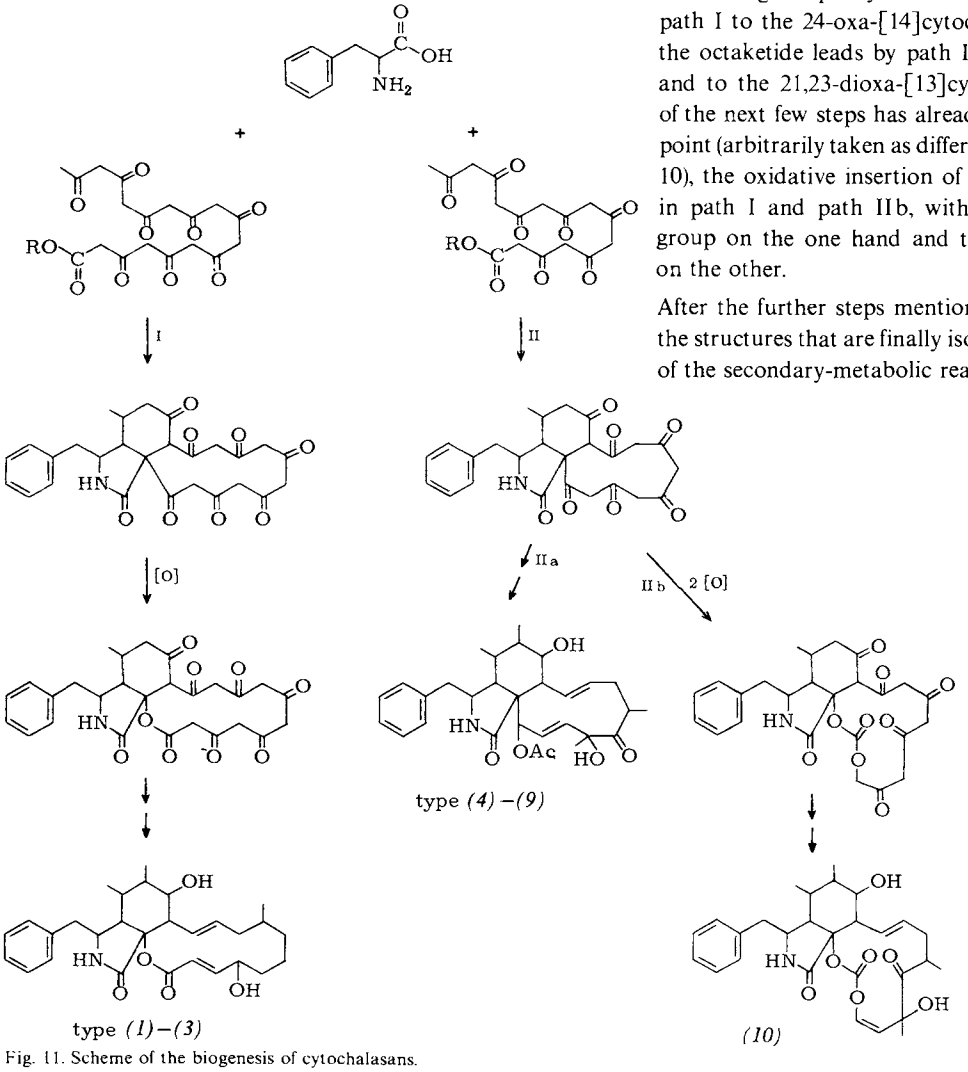


Fig. 11. Scheme of the biogenesis of cytochalasans.

The proposed scheme could be confirmed by elucidation of the biogenesis of cytochalasin D *(5)* and cytochalasin E *(10)*.

On the basis of the biogenetic scheme, we would venture to postulate the existence of further basic types of cytochalasans, possibly from block mutants of the microorganisms mentioned. One possibility would be a [13]cytochalasan, *i.e.* phomin *(2)* without the inserted oxygen[*], or a 28-oxa-[12]cytochalasan, *i.e.* cytochalasin D *(5)* with only one inserted oxygen.

Another question that would have to be answered is whether the carbocyclic cytochalasans are direct precursors of the heterocyclic cytochalasans.

6. Biological Effects of the Cytochalasans

All cytochalasans inhibit cytoplasmic cleavage in mammalian cell cultures, but differ in the intensity of their action.

In the presence of phomin (cytochalasin B) *(2)* (1 μg/ml), normal mitosis occurs in mammalian cells, but cytokinesis, *i.e.* the cleavage of the cell plasma, is blocked[12, 24].

Prolonged contact with phomin *(2)* leads to the formation of large multinucleate cells. It is interesting to note here that instead of doubling the number of nuclei per cell, each mitosis gives only one new nucleus.

High concentrations of phomin *(2)*, around 10 to 20 times the quantity required for the inhibition of cytokinesis, leads to ejection of the cell nucleus. Provided this process is not yet complete, it can be reversed in exactly the same way as cytostasis by removal of the cytochalasan; the processes are reversible.

Another general effect of the cytochalasans is their action on cell movement. Phomin *(2)* inhibits the movement of L cells. The cell margins become quiescent, and the cell ultimately assumes the shape of a thin disk. In the case of cytochalasin E *(10)*, the cells assume a broad scalloped margin.

The range of further biological activities of the cytochalasans is considerable. Phomin *(2)* blocks the development of tubular glands in the chick oviduct[25] and influences the development of normal branching in the salivary gland of the mouse[26].

Other processes affected included phagocytosis[27, 28] platelet aggregation[29, 30], breakdown of blood clots[29–31], production of cytoplasmic streaming[32], tail resorption in tunicate larvae[33], contraction of the myocardium[32], thyroid secretion[34], and the release of growth hormones[35].

Because of the strong anti-edemic and abscess-inhibiting properties of cytochalasin D *(5)* in rats, the Japanese workers have patented the production of the compound (from the microorganism mentioned) and its use in therapy[36]. Application in human medicine does not appear to be ruled out.

Finally, one might ask how the chemistry of the cytochalasans will develop in the future.

Unsolved problems include the biogenesis of the [11]cytochalasans and the 21,23-dioxa-[13]cytochalasans, as well as the isolation of larger intermediate products in the biogenesis of phomin *(2)*. Other points of interest (admittedly purely academic) would be attempted total syntheses and above all the discovery of new cytochalasans, possibly with the as yet unknown basic skeletons postulated above.

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[*] Note added in proof: In the meantime we have succeeded in isolating the postulated [13]cytochalasan, deoxaphomin, as well as two further metabolites of this type.

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Mechanistic Analysis of Solution Reactions by Non-Isothermal Calorimetry

By Erhard Koch[*]

For the rapid kinetic and energetic analysis of reactions in solution ($\tau_{20\,c} > 10^{-4}$ s) by differential thermal analysis (DTA), the following thermogram parameters are defined as characterizing the start of the reaction: 1. initial temperature, 2. activation energy of the initiation reaction. In conjunction with the shape index (asymmetry of the DTA curve) and the half width of the DTA curve referred to standard physical conditions (cell constant, heating rate, and temperature difference), these quantities allow a simple distinction between one-step reactions of first and second order and composite reactions. It is possible to recognize whether a process involves parallel, successive, or equilibrium reactions, or combinations of these. The reaction mechanism can be clarified in many cases by measurements at various concentrations and heating rates and by discussion of the enthalpy values. The shortened method described in this report for the evaluation of the thermograms was derived with the aid of an analog computer and checked experimentally.

1. Introduction

Non-isothermal thermal measuring methods have the advantage over many other investigation methods of universal applicability. In one measurement they cover both the energetic and the kinetic aspects of any system investigated. The non-isothermal thermal analysis of reactions is therefore an ideal complement, in principle, to all methods involving the analysis of substances, and its result, the thermogram, is a sort of "reaction-analytical placard".

However, thermal measurements in solution have not so far been extensively used, one reason being that the relations between the reaction parameters and the measured temperature are not simple, and the time that had been saved was therefore lost again because of the complicated evaluation.

The most common thermal investigation method is differential thermal analysis (DTA)[1]. However, the use of this method for the precise kinetic analysis of solution reactions calls for calorimetric operating conditions[2-4]:

1. dilute solutions,

2. stirring of the sample solution and of the reference solution to avoid temperature differences within the solutions,

3. temperature measurement in both solutions.

Equipment designed with these factors in mind lead, for one-step reactions, to thermograms that satisfy an equation derived by *Borchardt* and *Daniels*[2,3]:

$$k = \left[\frac{V|\Delta H|}{C_p}\right]^{n-1} \frac{c \cdot \theta + \frac{d\theta}{dt}}{\left[c \int_t \theta\, dt - \theta\right]^n} \qquad (1)$$

k = reaction rate constant
n = reaction order
V = volume of sample solution
ΔH = molar enthalpy of reaction
C_p = heat capacity
θ = temperature difference between sample solution and reference solution
c = kinetic cell constant

For fractional values of n, the evaluation with the aid of this equation yields formal activation energies and frequency factors, but no information on the manner in which the individual processes are linked. It cannot be applied to more complicated processes. An evaluation method for such processes is described below. This method is based on breakdown into individual processes, and allows the accurate and fast interpretation of many types of complicated thermograms without the use of complicated mathematics. Its basic principles are also applicable to other non-isothermal investigation methods.

2. Thermograms and their Characterization

The evaluation of the DTA curves ($\theta = f(t)$, $T = T_0 + \alpha \cdot t$) presents a number of problems, since both physical equipment parameters and chemical parameters are involved in a mathematically complicated combination. However, the chemist will be interested only in the chemical consequences. To study the effects of all the parameters, we developed an analog computer program, which allows the investigation even of complex mechanisms (up to four simultaneous reactions)[5]. The results of these investigations suggest the use of five independent curve parameters for the characterization of each individual thermogram signal (cf. Fig. 1):

1. total area,

2. initial temperature,

3. initial activation energy,

4. shape index,

5. half width.

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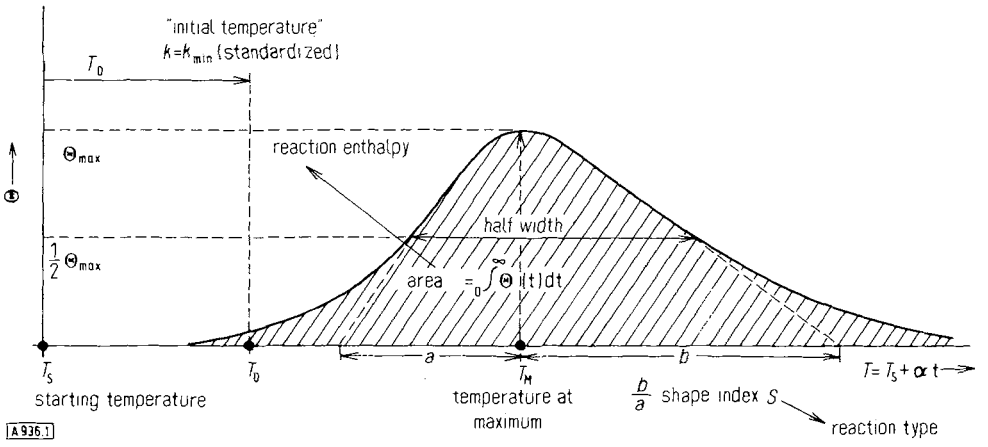


Fig. 1. Characteristic parameters of thermograms with one signal.

2.1. Total Area $\int_0^\infty \theta\,dt$

The total area between a DTA curve $\theta=f(t)$ and the zero line is used for the calculation of the heat of reaction[1,4], while the area after a time t until the curve has reached the base-line ($t=\infty$, integral in eq. (1)) is a measure of the concentration of reactive substance(s) still present.

The kinetic conditions at the start of the reaction are especially clear, since the time-dependent partial integral practically still agrees with the total integral, and because of the resulting constancy of the denominator in eq. (1), the reaction order does not yet have any effect. As will be shown later, it is also advantageous for other reasons to define the kinetic parameters in this region of the curve.

2.2. Initial Temperature T_0

At the first strong deviation of the curve from the zero line, a reaction should generally be strongly favored. Whereas in isothermal kinetics the reactivity of a substance is normally described by a reaction rate constant, a more suitable description for non-isothermal kinetics is a temperature that corresponds, *via* the Arrhenius equation, to a fixed standard rate constant[5]. Since the rate constant at the beginning of a DTA curve is always of the same order of magnitude ($k=10^{-6}$ to $10^{-4}s^{-1}$)[*], we took as our reference value $k_{min}=10^{-5}s^{-1}$. For pseudo-unimolecular processes, this value must be divided by the concentration of the reactant that is present in excess in order to obtain the true bimolecular constant. In comparison with the "peak temperature" T_m at the maximum, which is easier to determine, such an initial temperature has the advantage that it is independent of the thermal conductivity in the initial region and allows direct comparison of reactivities[5]. For the range of solution reactions, therefore, a temperature defined in this way would facilitate the comparison[6,7] and the documentation of results obtained with different DTA equipment.

For apparatus of the calorimetric "Borchardt-Daniels type", the initial temperature for the "k_{min}" defined above is found purely empirically from the temperature T_0' for the first strong deviation of the curve from the zero line and from the signal height L to be

$$T_0 \approx T_0' - 7 + 0.12 \cdot L - \frac{32}{L} - \frac{0.18}{c} \qquad (2)$$

(maximum error ± 3°K), L = signal height in mm

2.3. Initial Activation Energy

At the beginning of the DTA curve, eq. (1) gives a simple relation for the activation energy from two points on the curve ($T_1, \theta_1, d\theta_1/dt$ and $T_2, \theta_2, d\theta_2/dt$):

$$E_0 = R \cdot \frac{T_1 \cdot T_2}{T_2 - T_1} \ln \frac{c\,\theta_2 + d\,\theta_2/dt}{c\,\theta_1 + d\,\theta_1/dt} \qquad (3)$$

From T_0 and the E_0 calculated from eq. (3), the "initial frequency factor" ($k_{\infty 0}$) is obtained *via* the Arrhenius equation:

$$\lg k_{\infty 0} = \frac{\lg e}{R\,T_0} \cdot E_0 + \lg k_{min} \qquad (4)$$

2.4. Shape Index S

This quantity describes the asymmetry of the curve[8], and is related to the type of reaction taking place (Fig. 1). For the case of constant heating rate, *Kissinger* derived the relation

$$S = 0.63\,n^2 \qquad (5)$$

but this becomes increasingly inaccurate for DTA in solution and at n values >1[5,8-11]. The shape index also depends on the cell constant c and on the heating rate[5,12]. If the S value is to be used as a criterion of the (apparent!) reaction order, therefore, it must be corrected to standard conditions with regard to these quantities and to a vanishingly small temperature difference between the sample solution and the reference solution. Suitable correction tables can be constructed with the aid of an analog computer[5]. However, the measuring technique can also be designed to maintain this latter condition by additional heating as in the "differential scanning calorimeter".

[*] The following statements are valid for the heating rate 1.5°C/min.

Under the standard conditions chosen here, *i.e.* $c=0.18\ \mathrm{min}^{-1}$, $dT/dt=1.5\,^{\circ}\mathrm{C/min}$, $\theta_{max}\rightarrow 0$, S assumes a value of 0.65 for a first-order reaction, but the value of 1.2 found for a second-order reaction is only about half of the value expected from eq. (5). However, measurements on numerous one-step reactions have shown that this value is evidently typical of second-order reactions.

2.5. Half Width *h*

This last curve characteristic can be read off directly. For a constant sample heating rate, it can also be used for the determination of the reaction type.

3. Half Width in One-Step Processes

Our numerous experiments and model calculations show that the following characteristic relation exists between activation energy, action constant, and the half width corrected to standard conditions for a first-order reaction

$$M_1 = \frac{E}{h(\lg k_x - \lg \tilde{k})^2} \approx \text{const.} = 4.2 \cdot 10^{-3}\ \text{kcal/mol} \cdot {}^{\circ}\text{K} \qquad (6)$$

$\log \tilde{k}$, with a value of -3, roughly corresponds to the rate constant at the time of the maximum of θ. The relation can also be derived purely mathematically.

On introduction of the temperatures T_1 and T_2 for which $\theta = {}^1/_2\,\theta_{max}$ and the corresponding rate constants k_1 and k^2 into the Arrhenius equation (4), gives $T_2 - T_1 = h$ and, after some rearrangement,

$$\frac{E}{h(\lg k_x - \lg k_1)(\lg k_\infty - \lg k_2)} = \frac{R}{\lg e \cdot \lg \frac{k_2}{k_1}} \qquad (7)$$

It can be shown that $\log k_2/k_1$ is practically independent of E and $\log k_\infty$. For this purpose, the Arrhenius equation is combined with the solution of the differential equation (8), which describes the balance between heat produced and heat dissipated[13]:

$$\frac{d\theta}{dt} = \frac{1}{C_p} \cdot \frac{dq}{dt} - c \cdot \theta \qquad (8)$$

For $\theta(t)$ one obtains an explicit expression with integrals, which become soluble only with the introduction of justified simplifications[11], and finally give the equation (6).

For first-order one-step reactions, the activation energy can be calculated directly *via* eqs. (4) and (6) from the half width and the initial temperature.

In second-order reactions, it has been found that M_1 is no longer constant for the same range of frequency factors, but the following quantity derived from M_1 becomes a constant whose value is approximately twice as large:

$$M_2 = M_1 \cdot \sqrt{\lg k_x} \approx \text{const.} = 9 \cdot 10^{-3}\ \text{kcal/mol} \cdot {}^{\circ}\text{K} \qquad (9)$$

The M_1 and M_2 defined in this way are auxiliary quantities derived from h, which are evidently similar to the shape indices in the mechanistic information that they provide. As will be shown later, however, they do not repeat the information given by the shape indices, but lead to further specification. We therefore suggest the names "reaction type index" for M_1 and "second reaction type index" for M_2.

4. Influence of a Second Reaction

Let us confine our attention for the moment to two reactions having the same enthalpy. Let one of these begin somewhat earlier in the DTA, *i.e.* have a lower T_0. The second reaction may then be regarded as a perturbation of the first, so that it can be disregarded at the beginning of the curve, and E_0 can be calculated from eq. (3) for the first reaction.

As the process continues, the second reaction will become either increasingly important or, if its activation energy is lower, increasingly unimportant. In the former case, it may be assumed that the half width and/or the shape index will be different from those of the first reaction. For a consecutive reaction that is not yet so much slower that it gives a second signal, for example, broadening of the signal is to be expected. For a condensation reaction between the product and the educt, on the other hand, the additional consumption of the starting material leads us to expect a decrease in h, *i.e.* an increase in M_1 or M_2 as against the constant values indicated in Section 3.

All reaction mechanisms can be built up from first-order one-step processes or processes of the bimolecular type $A+B\rightarrow C$. To include all conceivable reactions, we therefore constructed sets of model curves for all combinations of two first-order or second-order one-step processes (cf. legend to Fig. 2). As a standard reaction, we stored a reaction with the following data in the analog computer:

$$E = 15\ \text{kcal/mol}, \quad k_x = 10^{10.2}\ \text{s}^{-1}$$

$\alpha = dT/dt$, c, and θ_{max} corresponded to the standard conditions. For the second reaction, E and T_0 were varied within the following ranges for all mechanisms:

$$6 < E_2 < 20\ \text{kcal/mol}, \quad -30 < T_{02} - T_{01} < +30\,^{\circ}\text{C}$$

Abnormally high or low frequency factors ($\log k_x > 15\,\text{s}^{-1}$ or $< 5\,\text{s}^{-1}$) were disregarded. Bimolecular initiation reactions were programed for the initial concentration of 1 mol/l.

We thus obtained a set of 20—40 individual curves for each mechanism, and the shape indices and reaction type indices were calculated for these curves. To illustrate the dependence on the basic types of mechanism, we choose a diagram with the shape index S as the linear abscissa and M_1 as the linear ordinate (see Fig. 2, lower left field). For M_1 values that are lower by more than the error limit ($\approx 5\%$) than the typical value for first-order reactions, M_1 is replaced by M_2 in a downward continuation

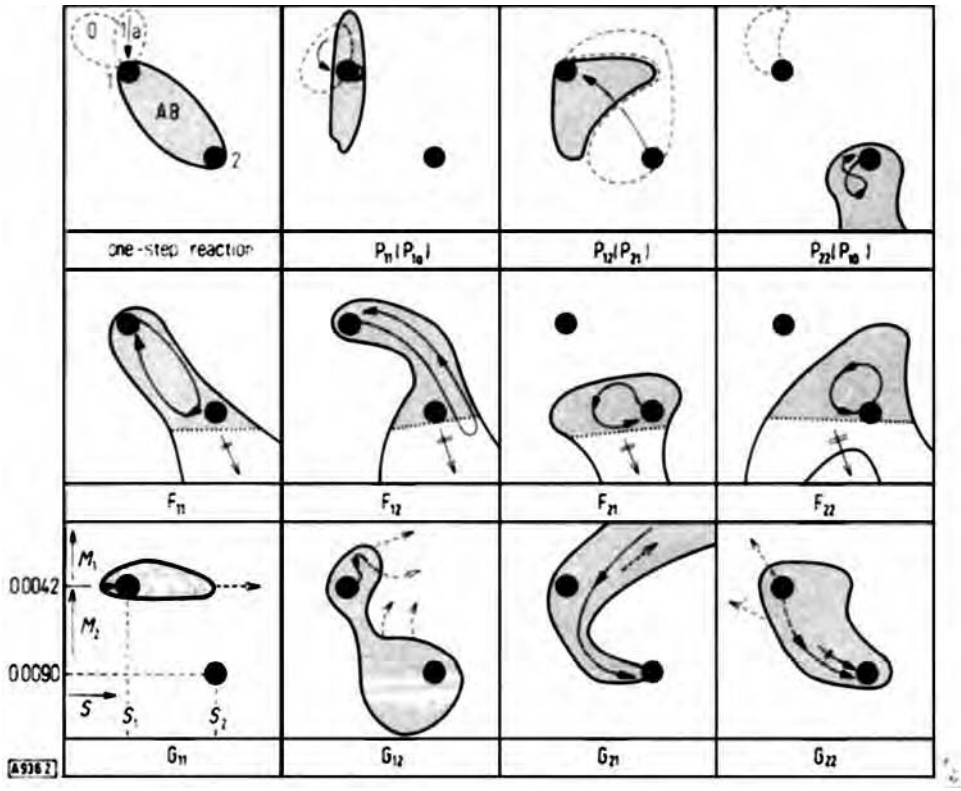


Fig. 2. Mechanistic analysis of thermograms.
⇸ splitting into two signals;
⇢ disappearance of signals;
→ curves for $k_{,2}=10^{10.2}\ s^{-1}$;
┈ boundaries of the "mechanistic regions";
( ) the same, mechanism designation in parentheses, *e.g.* (P_{21}).

Designation of mechanism types involving two reactions

0: Formal zeroth order reaction (*e.g.* catalytic).
1: First-order individual reaction.
1a: Autocatalytic reaction $A \xrightarrow{+B} 2\,B$ (ideal type).
AB: Bimolecular reaction $A+B \rightarrow C$.
2: Second-order individual reaction ($[A]=[B]$).

P_{pq}: Parallel reactions $A \begin{matrix} \nearrow B \\ \searrow C \end{matrix}$.

First index = Order of reaction with lower T_0 (=0, 1, or 2);
second index = order of reaction with higher T_0 (=0, 1, or 2);
index *a* = bimolecular condensation of B with A;
index *x* (possibly also *y*) first or second order.

F_{pq}: Successive reactions $A \rightarrow B \rightarrow C$.
Indices as above, but first index always corresponds to the initial reaction.

G_{pq}: Equilibrium reactions $A \rightleftharpoons B$.
First index always corresponds to the forward reaction.

U_{pq}: Kinetically independent reactions $A \rightarrow C$, $B \rightarrow C$ or D.
Indices as for parallel reactions.
The regions here are similar to those for successive reactions. Reaction types in parentheses are not very pronounced.

of the same scale. The ranges for the various basic mechanisms are given in Figure 2. The curve for $k_{,2}=k_{,1}=\text{const.}=10^{10.2}\ s^{-1}$ with a continuous increase in E_2 are also shown in the figure. As one moves along these curves in the direction of the arrow, the second reaction makes a steadily decreasing contribution to the overall process; as is to be expected, the curve for parallel reactions (= P) finally arrives at the point for the corresponding first-order or second-order one-step initiation reaction. For secondary reactions (= F) it also emerges from this point for the other extreme case of a much faster second reaction, and finally, after the splitting of the thermogram into two signals, returns to it for the first signal.

For a thermogram that has not yet been interpreted, this gives a clear criterion of whether or not a pure one-step reaction is involved. T_0, S, and h are found from the thermogram, E_0 is calculated, S and h are corrected, and the M_1 (or M_2 if $M_1<0.004$) calculated *via* $\log k_{x0}$ is plotted as a function of S. If the point obtained in this way lies in the regions for a first-order or second-order one-step reaction, which are slightly oval because of the error limits, the observed reaction is not appreciably perturbed by side reactions. In this case the initial activation energy E_0 is also identical with the overall activation energy calculated from h and T_0 or by other methods, *e.g.* computer simulation. If the point lies outside the one-step regions, however, one can see immediately which basic mechanisms are possible and which are not.

The situation for two reactions with different enthalpies can also be simulated by calculations. Kinetically and qualitatively, on the basis of eq. (4), an increase in the enthalpy of the second reaction has an effect similar to that of a depression of its initial temperature T_{02}.

5. Hints for Practical Use

The diagnosis method described here can be applied to any individual signal of a thermogram, but because of the overlap of the "regions" (Fig. 2) it very often leaves several possible mechanisms open. The following methods may be used to obtain more specific information[4, 5]:

1. Analyses are carried out at a lower heating rate. For secondary reactions (= F), equilibria (= G), and independent reactions (= U), this causes the points in the diagram to move toward the lower diagram border at first, and

Table 1. Asymptotic behavior of the mechanism coordinates of the basic mechanisms with increasing heating rate or concentration (cf. Figs. 2 and 3).

	End type	Parallel reactions 11	12	21	22	1a	Secondary reactions 11	12	21	22	Equilibria 11	12	21	22	Independent reactions 11	12	21	22
Diminution of $dT/dt = \gamma$	1	●	●			●	⊙	⊙	○		●	●			⊙	⊙	○	
	2			●	●			○	⊙	⊙		○	●	●		○	⊙	⊙
Increasing concentration	nc	●			●	●	●			●	●			●	●			●
	1		●	●				●	○			+	○			○	○	
	2								⊙				●			⊙	⊙	

nc: No change
● appropriate mechanism;
⊙ appropriate mechanism, but signal splitting;
○ behavior of the second signal formed;
+ disappearance of the signals.

this is followed by signal splitting and a movement back into the corresponding one-step regions. For parallel reactions (= P), on the other hand, the points converge toward the region of the initiation reaction (Table 1).

2. The measurements are carried out at a higher concentration. Second-order reactions are favored in this way, and their initial temperatures are depressed. The convergence behavior shown in Table 1 is thus found for the various types.

Superimposed equilibria (= G) can be considered only if the first signal clearly runs into a second. If the reverse reaction has a much lower T_0 than the initiation reaction, the measured effects may be partly compensated. Since ΔH_1 and ΔH_2 must have different signs but practically equal absolute values, the temperature differences may be very small, but they can be increased again by separation of the reactions (reduction of the heating rate).

For more complicated mechanisms, several signals usually appear in the thermograms. The results of the single-signal analysis just described also provide the basis for a reaction separation based on the principles mentioned for each isolated group of signals, *i.e.* splitting into further individual signals.

Further aids in the reaction analysis are the addition of interceptor reagents (introduction of bimolecular reactions) and the replacement of a solvent that takes part in the reaction by an inert solvent (elimination of pseudo-unimolecular reactions).

After extensive separation of the reactions and establishment of the individual types, the overall reaction mechanism can be built up from parallel-step and one-step reactions.

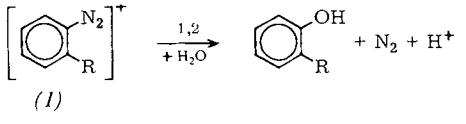
Since the thermodynamic data of all the individual steps can be obtained with the aid of an analog computer after the mechanism has been elucidated, it is then possible to confirm intermediates whose structures have been formulated both by means of thermograms of model substances and by comparison of the kinetic and energetic data.

6. Examples

Systems whose behavior is known will now be used to illustrate the application of the analytical method in accordance with the arrangement of Table 2. The positions of the examples in the mechanism diagram can be seen from Figure 3.

6.1. First-Order Reactions

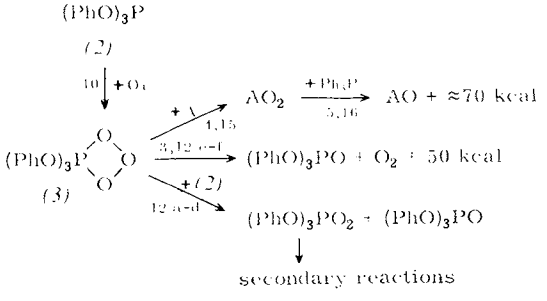
A test reaction that is repeatedly used for DTA investigations is the decomposition of arenediazonium salts with elimination of N_2 in dilute acids[2, 3, 5, 14, 15] (examples 1 and 2).



(1)

As Figure 3 shows, the positions of the points in the M/S diagram correspond, within the error limits, to an only slightly perturbed first-order reaction.

The unstable ozonide *(3)* obtainable from ozone and triphenyl phosphite *(2)*[16, 17] (Scheme 1) acts as an oxidizing agent at low temperatures[18, 19] and converts olefins into hydroperoxides, some of which have so far been obtainable only by photosensitized oxygenation[20–23].



Scheme 1.

Its decomposition (example 3) proceeds exclusively as a first-order process at sufficiently low concentrations.

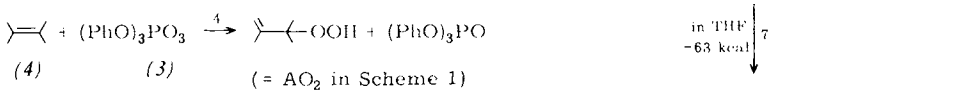
On addition of a large excess of tetramethylethylene *(4)* at −90 C, this acts as a scavenger, and only the bimolecular reaction 4 with hydroperoxide formation then occurs.

Table 2. Kinetic and mechanistic analysis of thermograms.

No.	Reactants [mol/l]	T_0	E_0	S	$M_1(M_2)$	Possible types
1	0.3 *(1)* (R = H) in CH_2Cl_2	304	30	0.71	39	1 $(P_{x_1}F_{11})$
2	0.3 *(1)* ($R = CH_3$) in CH_2Cl_2	293	28	0.73	40	1 $(AB.P_{21}F_{11})$
3	0.1 *(3)* in CH_2Cl_2	245	17	0.69	40	1
4	0.84 *(4)* + 0.08 *(3)* in CH_2Cl_2	202	5	0.61	50	1 $P_{11}P_{1a}$
5	0.037 *(5)* + 0.1 Ph_3P in CH_2Cl_2	194	7.6	0.90	40	1 $AB\,P_{12}P_{21}$
6	0.086 *(5)* in CH_3OH	258	19.6	0.68	41	1
7	0.12 *(5)* in THF	286	22.5	0.64	(130)	$AB\,P_{1x}F_{11}$
8a	0.04 *(8)* in CH_3OH	258	19.5	0.72	45	1 $(F_{1x}P_{2x})$
8b	1 aniline + 1 $NaNO_2$ + 1 HCl, then + 7 NaN_3 (in CH_3OH + 20% H_2O)	272	24	0.63	40	1
9	1.22 *(9)* in $HOCH_2CH_2OCH_2CH_2OCH_3$	419	26.6	1.13	(92)	2
10	0.05 *(2)* + 0.05 O_3 in $CClF_3$	125	4.5	1.2	(96)	2 (AB)
11a	1.4 *(10)* + 0.5 *(11)* in THF	294	17	0.98	(130)	$AB(P_{12}F_{1x}F_{22}G_{21})$
11b	0.1 *(10)* + 0.1 *(11)* in toluene	239	13	1.68	51	$G_{21}F_{1x}$
12a	0.1 *(2)* + 0.025 O_3	192	9.5	0.74	(120)	$AB\,P_{12}F_{11}F_{2x}G_{2x}$
12b	0.1 *(2)* + 0.050 O_3	195	≈ 10	0.75	(72)	$P_{22}F_{2x}G_{12}$
12c	0.1 *(2)* + 0.075 O_3	196	7.8	0.80	(90)	2 $P_{2x}F_{xy}G_{12}G_{2x}$
12d	0.1 *(2)* + 0.100 O_3 (in CH_2Cl_2)	200	8.0	0.72	(110)	$AB\,P_{21}F_{xx}F_{21}G_{2x}$
12e	0.1 *(2)* + 0.125 O_3	222	11.4	0.65	50	1 $(P_{1x}P_{01}F_{1x})$
12f	0.1 *(2)* + 0.150 O_3	223	15.6	0.70	43	1
13	0.85 *(13)* + 0.034 *(3)* in CH_2Cl_2	215	11.4	0.51	(70)	$P_{11}(P_{12})$
14	0.1 *(14)* in CH_3OH	214	11.2	1.3	48	P_{21}
15	0.61 *(16)* + 0.04 *(3)* in CH_2Cl_2	226	6.7	0.45	90	0 $P_{10}P_{1a}(P_{11})$
16	0.04 *(17)* + 0.1 Ph_3P in CH_2Cl_2	183	10.1	2.0	(65)	$P_{22}F_{1x}F_{22}G_{12}(G_{22})$
17	0.05 $PhNH_2 \cdot HCl$ + 0.05 $i\text{-}C_5H_{11}NO_2$ + 0.05 NaN_3 in methanol/H_2O (7:1)	α 188 β 220 γ 288	10 10.3 19	1.0 0.88 0.78	80 (83) 46	G_{21} $P_{1x}F_{1x}$ 1 $(P_{1x}P_{21})$
18	4.5 *(13)* + 0.05 CH_2N_2 in ether	220	8.5	0.64	85	1a $P_{01}P_{11}P_{1a}(F_{11})$
19	0.14 *(19)* + 3 H_2O in THF	α 267 β 280	70 18.9	1.2 0.8	160 (12)	$P_{21}F_{xy}$ (1) $AB\,F_{11}F_{2x}$

α, β, γ: first, second, and third maxima (from low temperature);
T_0: initial temperature [K];
E_0: initial activation energy [kcal/mol];
S: corrected shape index;
M_1, M_2: reaction type indices [10^{-4} kcal/mol·K].
Types: See legend to Fig. 2.

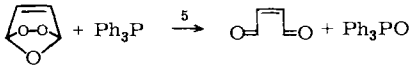
Because of the pseudo-unimolecular character of the reaction, a first-order reaction is observed in practice:



(4) *(3)* (= AO_2 in Scheme 1)

(= A in Scheme 1)

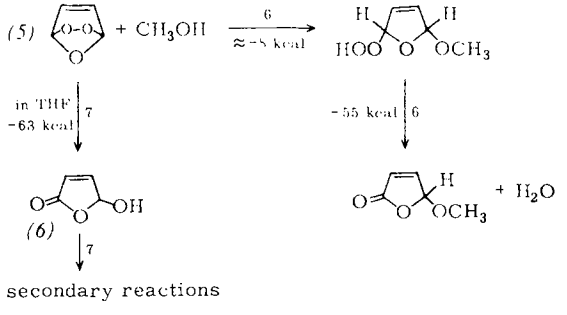
If triphenylphosphane is added to a photochemically or thermally prepared compound AO_2, *e.g.* the epidioxydihydrofuran *(5)*, the bimolecular redox reaction[4, 20, 24] (cf. Scheme 1) can also be observed (example 5).



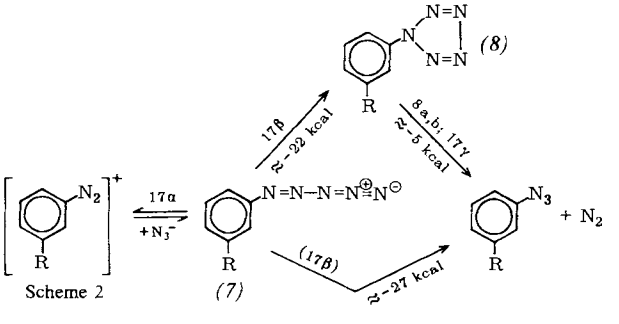
(5) (= AO_2) (= AO)

Another example of a pseudo-unimolecular reaction is the addition of methanol to the ozonide-like peroxide *(5)*, which is followed by an immeasurably fast elimination of water[3, 4, 24] (example 6).

The reaction begins much later in tetrahydrofuran (example 7). Because of the perturbed course of the decomposition, *(6)* is no longer the only end product; secondary reactions, such as the formation of dimers, also occur.



The pentazole *(8)* formed from diazotized aminobenzene and azide[25], after isolation and dissolution in methanol, exhibits an almost unimolecular decomposition (example 8a; Scheme 2).



Scheme 2 (7)

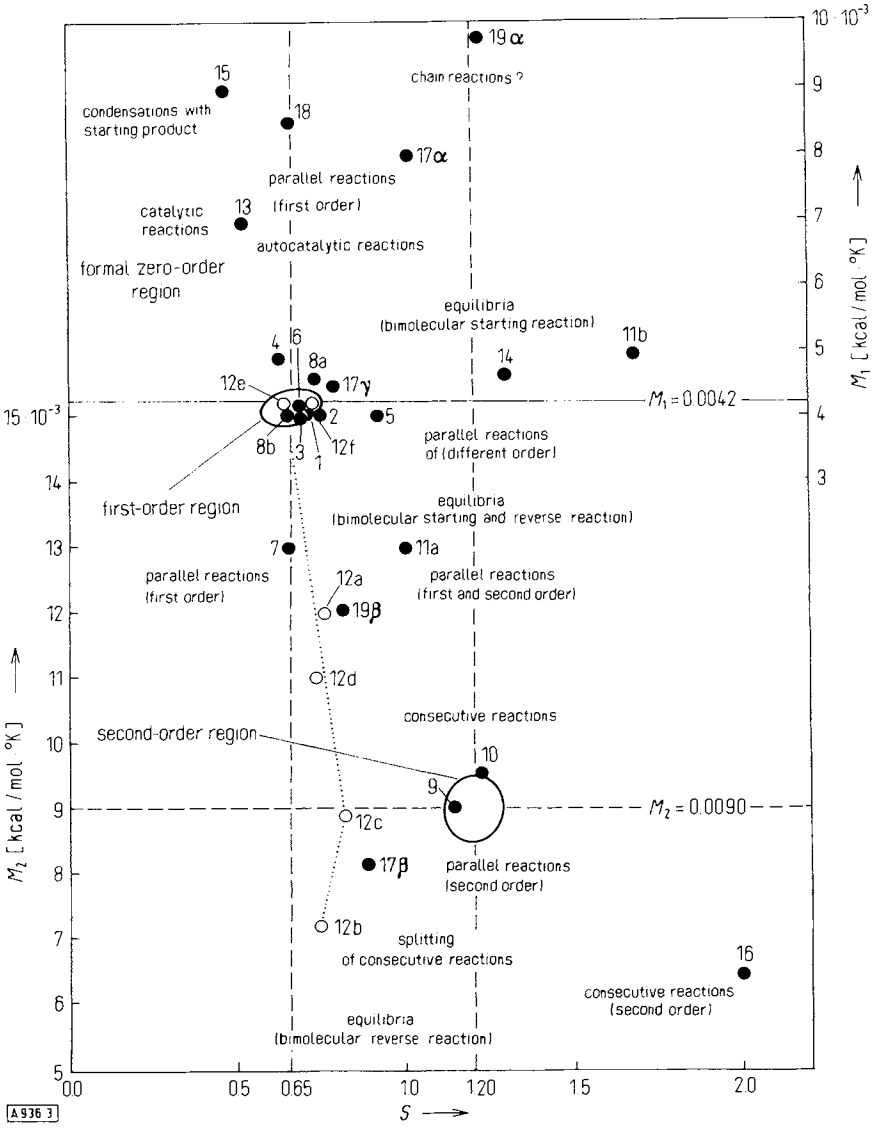
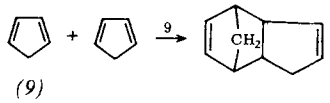


Fig. 3. Positions of systems investigated in the mechanism diagram. Numbering of examples as in Table 2 and by the reaction arrows. The explanatory text can only indicate the positions of typical regions from Fig. 2.

If instead of isolating the pentazole one examines the reaction mixture itself (example 8b), the purer course of the decomposition reaction indicates that the *p*-ethoxyphenylpentazole used in example 8a had evidently undergone partial rearrangement during isolation.

6.2. Second-Order Reactions and Bimolecular Reactions (Type AB) with Non-Equimolar Ratios of the Components

The dimerization of cyclopentadiene *(9)*[26,27] can be followed thermally in solution (example 9).

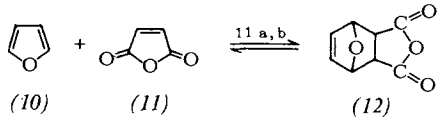


(9)

It is evidently not perturbed under these conditions by further condensation or cleavage back into the monomer.

The formation of the above-mentioned triphenyl phosphite ozonide *(3)* (Scheme 1) can be observed directly in solvents that allow investigation temperatures below −120 °C. With an equimolar ratio of the reactants, it practically follows second-order kinetics (example 10).

In bimolecular reactions, the influence of the molar ratio may be so strongly distorted by perturbations that the resulting M/S point no longer lies in the AB region of Figure 2 (examples 11a, b).



(10) *(11)* *(12)*

The formation of the Diels-Alder adduct *(12)*[28,29] is reversible, so that with an equimolar ratio of the reactants in dilute solution, the back-reaction already influences the first reaction signal.

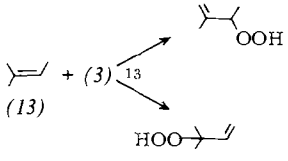
The influence of the molar ratio of the reactants on the type of reaction can be investigated in the system triphenyl phosphite/ozone (examples 12a—f, cf. Scheme 1). With much less than the stoichiometric quantity of O_3 (12a), the decomposition of the ozonide *(3)* is preceded by its

bimolecular reaction with excess phosphite *(2)* (cf. example 4, Scheme 1), but by further reaction steps (dimerization of the $(PhO)_3PO_2$ formed and disproportionation) *(3)* is ultimately regenerated, so that a second and a third signal appear. The activation energy of this interception reaction is only about 5.5 kcal/mol. With increasing addition of O_3 (examples 12b, c), the "mechanistic point" in Figure 3 approaches the second-order region. Because of the decrease in the concentration of *(2)* through the interception reaction, however, the start of this reaction is displaced toward higher temperatures (example 12d), so that the first maximum moves into the region of the unimolecular decomposition reaction (example 3). Finally, if ozone is present in excess (examples 12e, f), this reaction alone controls the process, and the first-order region is reached. The initial activation energy accordingly increases from about 8 to 15.6 kcal/mol, *i.e.* to roughly the value for the decomposition reaction (example 3).

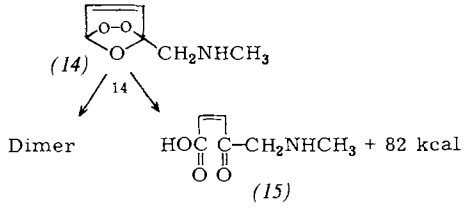
The following examples of *complex reaction types* are concerned with nearly all regions of Figure 3.

6.3. Complex Reactions

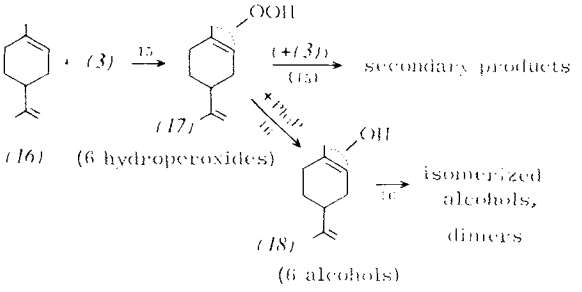
Two parallel first-order reactions give only one signal. The initial activation energy E_0 does not agree with activation energies in other parts of the curve. The half width h assumes anomalous values, while the shape factor S differs only slightly from the value for first-order reactions. This is shown by example 13, which has also been investigated preparatively[30, 31].



Parallel first-order and second-order reactions. The decomposition of the ozonide-like peroxide *(14)* of *N*-methylfurfurylamine (example 14) yields (*N*-methyl)glycylacrylic acid *(15)*[4, 32]. However, the direct formation of an isolable dimer is observed in the concentration range chosen here.



More than two parallel first-order reactions. The parallel formation of up to six hydroperoxides *(17)*, which undergo partial isomerization, by thermal oxidation of *d*-limonene *(16)*[20, 31, 33, 34] is a test case for the extension of the foregoing example to more than two processes. Because of the large excess of *(16)* (example 15), several parallel first-order reactions are to be expected. However, the "mechanistic point" appears in the upper limiting region of the P_{11} area, which is typical of condensation reactions with the educt or of autocatalytic processes. Secondary condensation steps cannot be ruled out in this example.



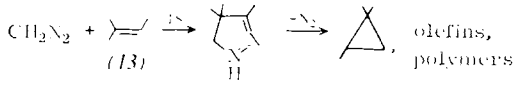
Six parallel reactions of type AB with secondary reactions. The hydroperoxides *(17)* formed in example 15 can be reduced with triphenylphosphane (example 16). A displacement from the P_{12}/AB region into the region of lower M but higher S values (Fig. 3) confirms that the reduction products isomerize or dimerize.

Equilibrium followed by parallel and secondary reactions. The formation and the decomposition of pentazoles *(8)* (Scheme 2) can be observed directly in solution. With a sufficiently low starting temperature (≈ 190 K), the thermograms of diazotized aniline salt solutions in methanol/water after addition of excess NaN_3 show three maxima, which are evidently due to the formation of the linear diazoazide *(7)* (example 17α), the cyclization of *(7)* to form the pentazole *(8)* (17β), and the decomposition of *(8)* (17γ = 8a, b).

Mechanistic analysis shows that the formation of *(7)* is probably an equilibrium reaction, and that a first-order or second-order reaction (which leads directly to the phenyl azide[25]) competes with the step leading to the pentazole *(8)* so that the yields of *(8)* do not nearly correspond to the feed. This can also be investigated quantitatively by measurement of the heat effect in the third step.

6.4. Occurrence of Free-Radical Steps and Chain Reactions

Example 18, the addition of diazomethane to the olefin *(13)* and the subsequent decomposition of the resulting pyrazoline[35, 36], leads into the boundary region of free-radical processes.

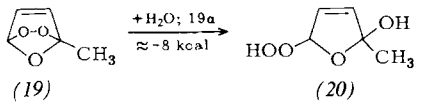


This raises the question, as yet unanswered, how far the arguments so far can be applied to free-radical mechanisms. The type determination leads in example 18 to condensation mechanisms, whereas pure consecutive reactions should be expected because of the excess of olefin. However, only one signal is present.

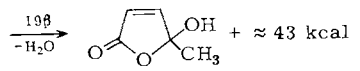
A further example raises a similar problem.

The addition of methanol to the unstable, ozonide-like epidioxydihydrofurans[4, 34] (cf. example 6), which has

become established even in preparative work in many cases, cannot be applied directly to water. In the example of the ozonide *(19)* (and also for *(5)*), instead, of a simple bimolecular step leading to the compound *(20)*, one finds a complicated sequence that evidently possesses chain character (example 19):



(19) *(20)*



(21)

Whereas the second maximum behaves normally, the first ascends so steeply that simple evaluation on the basis of the initial activation energy gives an unrealistically high frequency factor. The condition that the kinetics of the process must be determined initially by a single reaction is evidently no longer satisfied; even with the first strong deviation from the zero line, there is a reaction feedback, which must be considered by the methods of polymerization kinetics[138].

It has generally been found that abnormally high k_{r0} values (above 10^{16} s^{-1}) are always due to chain reactions or physical disturbances, *e.g.* separation of material. An extension of the model described here to chain reaction mechanisms seems conceivable.

7. Outlook

Two years ago, this journal published a report on the possibilities offered by low-temperature DTA, particularly in photochemistry, for the detection and investigation of unstable intermediates[4]. For all reacting systems, this method also yields numerous parameters, whose importance can be fully recognized by a mathematical analysis. In conjunction with the use of hybrid analog simulators, it presents ideal conditions for a complete reaction analysis even of systems whose reactions are still unknown.

The two-reaction model presented here leads to an evaluation method that is universally applicable and that should be particularly suitable for use in the search for new synthesis routes and in their optimization. Even for complicated processes, an analysis provides information about the conditions under which the thermodynamic data for the individual processes can be obtained by further experiments. The current rapid development of electronic measuring methods and of computer technology enables us to foresee where this road may finally lead, *i.e.* to the fully automatic reaction analyzer, which, after feedback between computer results, sample preparation, and reprograming of the measurement for each sample introduced, will print out the prevailing reaction scheme, with the data for all the steps. It will then remain for the chemist to insert the appropriate structural formulas for intermediates and final products, and to check whether and to what extent his proposed synthesis can be achieved.

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Iron-Sulfur Proteins: Structural Chemistry of Their Chromophores and Related Systems

By Ronald Mason and J. A. Zubieta[*]

Intensive studies of iron-sulfur proteins were begun only a decade or so ago but many biological and physicochemical data have since been accumulated and summarized[1-5]. As a result of the very recent X-ray analyses of the structures of rubredoxin[6], ferredoxin (*Peptococcus aerogenes*)[7] and the *Chromatium vinosum* high potential iron protein (Hipip)[8], it has become possible to review our understanding of the nature and function of the inorganic chromophores in these proteins; to relate these findings to 'model' systems of varying relevance; but of more general interest, to comment on redox processes in biological systems particularly with respect to what might be termed electron transfer—allosteric effects in metalloenzymes.

1. Summary of Iron-Sulfur Proteins and Their Properties

The proteins which will be discussed here are distinguished from other iron-containing proteins[9] in so far as the metals are not coordinated by the complex organic ligands found, for example, in heme-proteins[10] and the siderochromes[11]. In rubredoxin, the single iron atom is coordinated by four cysteine-sulfur atoms; the ferredoxins from plants and bacteria have iron atoms coordinated by cysteine-sulfurs and by 'inorganic' sulfide (labile sulfur).

The biological role of rubredoxin has not been completely clarified; that of the ferredoxins is electron transfer in processes as diverse as nitrogen fixation, photosynthesis, hydroxylation of steroids[12], reduction of sulfite by hydrogen[13] and the reduction of NADP by formate in *Sarcina ventriculi*[14]. More generally, iron-sulfur proteins are implicated in pyruvate reduction[15] and in succinate dehydrogenase from heart-muscle particles[16] (see Table 1).

Those relatively low-molecular weight iron-sulfur proteins with two to eight iron atoms and an equal number of labile sulfide ions per molecule are known as the ferredoxins and have redox potentials which allow them to function as cellular electron carriers on the hydrogen side of NAD or NADP[12]. This fact, together with their particular amino-acid composition, has formed the basis for the speculation that they were amongst the earliest of proteins to have evolved chemically[24,62]. The known amino-acid sequences of many plant and bacterial ferredoxins are such that, separately, they show strong homologies. More recently, and interestingly, the photosynthetic bacteria of the *Chromatium* type have yielded ferredoxins whose sequences and compositions are intermediate between bacterial and plant proteins. Thus the ferredoxin from *Desulfovibrio gigas* shows[43] a strong homology with bacterial ferredoxins for the residues 1—29 but the remaining part of the chain shows some resemblance to the sequences which define the plant ferredoxins; this protein is important, therefore, as a possible link between the ferredoxins derived from anaerobic fermentative bacteria and plants. It is assumed that the bacterial ferredoxins may have evolved through gene duplication from a proto ferredoxin of 29 residues[63], a speculation also relevant to the fairly precise twofold symmetry of the eight-iron ferredoxin molecule from *P. aerogenes* (see Section 2.3).

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2. Structural Chemistry of the Redox Centers in Iron-Sulfur Proteins

2.1. Rubredoxin

Through one of the most accurate structural analyses of a protein, *Jensen et al.*[6,64] have defined the nature and geometry of the redox center in rubredoxin (*Peptococcus aerogenes*) (Fig. 1). The oxidized protein can be regarded as a simple high-spin ferric thiol complex but the distortions from tetrahedral coordination geometry would not have been anticipated from the structural chemistry of simple four-coordinate complexes of iron(III). The ground state

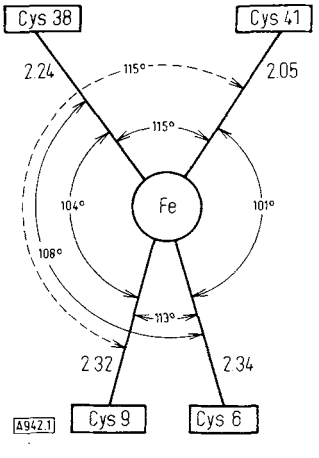


Fig. 1. Geometry of the iron-cysteine chromophore of rubredoxin (*P. aerogenes*) as determined from the 1.5 Å X-ray data (after *Jensen*, 1972; see Ref. [64]).

Table 1. Summary of iron-sulfur proteins and their properties [a, b].

Type	Organism	M.W.	Redox potential [V]	Number of electrons carried	EPR [c] oxidized	EPR [c] reduced	Ref.
1 Fe, 0 Sulfide Rubredoxin	Anaerobic, sulfate reducing, aerobic photosynthetic bacteria	≈ 6000	≈ −0.05	1	g=4.3, 9.0	None	[17–22]
	(*Pseudomonas oleovorans*)	(19000)					[23]
2 Fe, 2 S* Plant ferredoxin	Spinach; blue-green, yellow, green algae; primitive plants	11500	≈ −0.40	1	None	g=1.95	[24–33]
Putidaredoxin	*Pseudomonas putida*	12000	−0.23				[34]
Adrenodoxin	Mammals	13000	−0.34				[35–37]
Bacterial	*Azotobacter vinelandii* I	21000		1	None	1.94	
'ferredoxin'	*Azotobacter vinelandii* II	24000		1	None	≈ 1.94	[38]
4 Fe, 4 S*	*Chromatium* (HIPIP)	10000	+0.35	1	2.04	None	[39]
Bacteriaal	*Bacillus polymyxa*	9000	−0.37		None	1.94	[40]
	Desulfovibrio gigas	6000	−0.32	1	—	—	[41–43]
6 Fe, 6 S*	*Azotobacter vinelandii*	13000	−0.32	1	(Isolated	Partially Reduced)	[44–45]
		(20000)			≈ 2.00	~ 2.01	
8 Fe, 8 S*	*Azotobacter vinelandii*	14200	−0.42				[46]
Bacterial	*Chromatium*	9600			None	1.94	[47]
	Clostridial, Micrococcus Peptococcus	6000	−0.4 to −0.5	2	None	1.94	[48–53]
Molybdoproteins							
Xanthine oxidase 2 Mo, 8 Fe, 8 S* +2 Flavin	Mammals	275000			None in 'resting' state	1.97	[54–55]
Nitrogenase Fraction I							
2 Mo, 22–24 Fe–S*	*Cl. pasteurianum*	220000 (4 subunits, 2 each of 50000 & 60000)			4.3, 2.01 (native)	–	[56–58]
1 Mo, 17–18 Fe—S*	*Kleb. pneumoniae*	218000 (4 subunits, 2 each of 51000 & 60000)				4.3, 3.7, 2.015	[59, 60]
1 Mo, 33 Fe—S*	*Azotobacter vinelandii*	270000(2 types of subunits)			4.3, 3.67, 2.01	4.3, 3.67, 2.01, 1.94	[61]
Fraction II							
4 Fe, 4 S*	*Kleb. pneumoniae*	66800 (1 type of subunit, 34600)			None	1.94	[60]
	Cl. pasteurianum	55000 (1 type of subunit, 27000)					[58]

[a] For a more complete set of references and a similar tabulation, see Ref. [4].
[b] *Tsibris* and *Woody* [3] present a discussion of the physicochemical properties of the iron-sulfur proteins.
[c] The EPR data for these complexes is fully discussed by *Bearden* and *Dunham* [5].

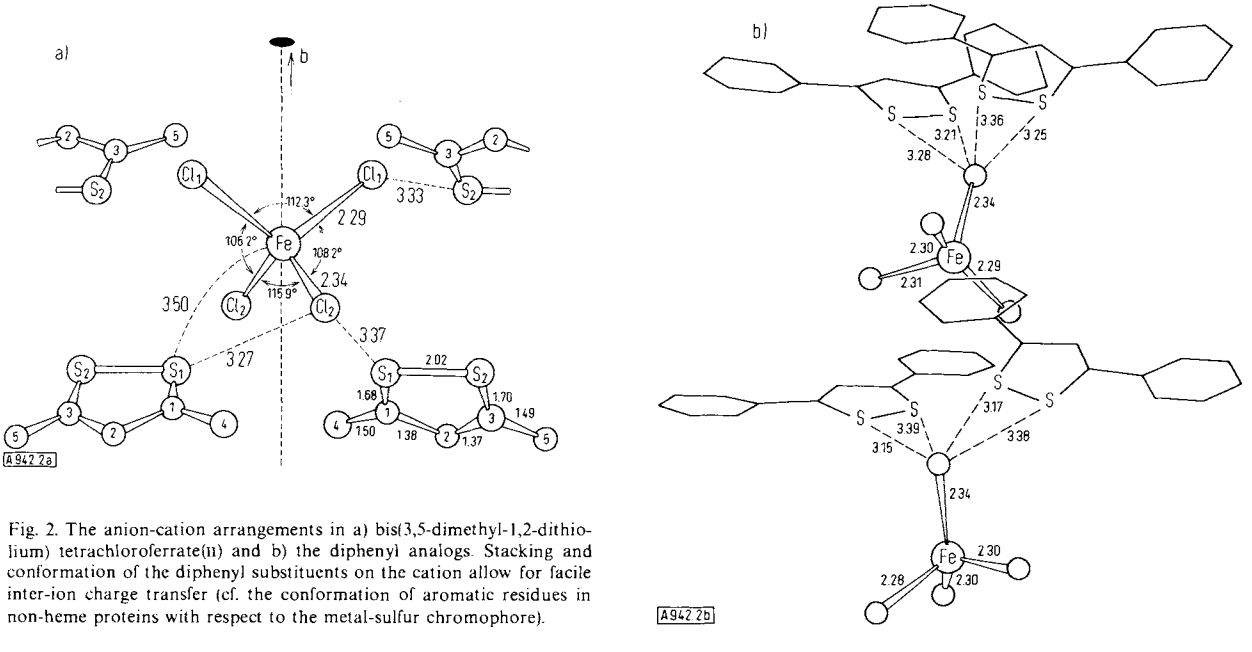


Fig. 2. The anion-cation arrangements in a) bis(3,5-dimethyl-1,2-dithiolium) tetrachloroferrate(II) and b) the diphenyl analogs. Stacking and conformation of the diphenyl substituents on the cation allow for facile inter-ion charge transfer (cf. the conformation of aromatic residues in non-heme proteins with respect to the metal-sulfur chromophore).

of a d^5 ion in a tetrahedral, high-spin complex is the orbitally non-degenerate $^6A_1$; thus simple crystal field theory predicts no Jahn-Teller distortion of the complex from T_d symmetry. High spin d^6 ions in a tetrahedral field have orbitally degenerate ground terms and the geometrical distortions from regular T_d symmetry are angular ones only, a feature which is also imposed on orbitally-non-degenerate ions by crystal packing effects[65]. The angular

distortions in the iron coordination sphere of oxidized rubredoxin must largely reflect the steric and electronic demands and constraints of the polypeptide chain. Isolated four-coordinate complex ions of Fe^{II} and Fe^{III} do not exhibit significant variation in the metal-ligand bond lengths but the variation in the Fe—S bond lengths in rubredoxin remind one, albeit qualitatively, of the situation in bis(3,5-dimethyl-1,2-dithiolium) tetrachloroferrate(II) and the diphenyldithiolium analogs of $[FeCl_4]^{2-}$ and $[HgCl_4]^{2-}$[66,67]. In these cases, the metal-ligand bond lengths vary by up to 0.08 Å and in a way which reflects *local* charge transfer interactions between the complex anions and the adjacent dithiolium cations (Fig. 2). The very short Fe—S bond length of 2.05 Å in rubredoxin may thus be due to some strong interaction with an adjacent electronegative group, a point to which we return in Section 3 in connection with the mechanism of the electron transfer processes.

The geometry of the chromophore in the oxidized rubredoxin is already, in the sense of angular distortions, intermediate between that which could be anticipated for isolated high-spin ferrous and ferric complexes; as such, it is relevant to discussions of the entatic theory[68,69] of enzyme catalysis. But the major stereochemical distortion is caused by specific non-valence interactions which could not have been anticipated by any considerations *ab initio*. Possible changes in the chromophore geometry during redox are discussed in Section 3.

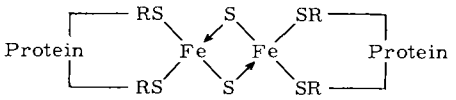


Fig. 3. Proposed structure for the redox centers in 2Fe-2S* proteins.

In the oxidized protein, each iron is in a pseudo-tetrahedral ligand field; they are both high spin ferric ions (S = 5/2), antiferromagnetically coupled to give a total spin, S, of zero[5]. Intuitively, this is not a surprising result but the spectroscopic data on the reduced protein provide convincing evidence that the two iron atoms are now, respectively, high spin ferric and high-spin ferrous ions (S = 2), antiferromagnetically coupled, giving a net total spin S = 1/2 for the dimeric iron-sulfur chromophore. It has been suggested that one electron reduction populates a metal orbital lying along the metal-metal bond axis and that electronic repulsion between the iron atoms may explain the low redox potentials of the binuclear chromophore. But a more general assessment of the electronic structure of the chromophore and the question of electron localization in the reduced protein can be developed from the structural data on other sulfur-bridged binuclear iron complexes (Table 2).

Table 2. Structural data of sulfur-bridged binuclear iron complexes.

Complex	Fe—Fe [Å]	Dihedral angle (between FeSS and Fe'SS) of the Fe_2S_2 bridge and formal oxidation state of the iron atoms		Electronic configuration (Fig. 4) and approximate Fe—Fe bond order		Ref.
$[(C_6H_5)CSFe(CO)_3]_2$	2.51	91.8°	+1	$(XZ_b)^2(Z_b^2)^2(XZ^*)^2(Z^{2*})^2(YZ)^2$ (non-bonding)^{12}	1	[70]
$[Fe(CO)_3(SC_2H_5)]_2$	2.54	95.2°	+1	$(XZ_b)^2(Z_b^2)^2(XZ^*)^2(Z^{2*})^2(YZ)^2$ (non-bonding)^{12}	1	[71]
$[Fe(CO)_3S]_2$	2.55	79.8° [b]	+1	$(XZ_b)^2(Z_b^2)^2(XZ^*)^2(Z^{2*})^2(YZ)^2$ (non-bonding)^{12}	1	[72]
$[Fe(SR)(S_2CSR)_2]_2$ [a]	2.61	180°	+3	$(XZ_b)^2(Z_b^2)^2(XZ^*)^2(Z^{2*})^2(YZ)^2$ (non-bonding)^8	1	[73]
$[Fe(NO)_2(SC_2H_5)]_2$	2.72	180°	−1	$(XZ_b)^2(Z_b^2)^2(XZ^*)^2(Z^{2*})^2(YZ)^2$ (non-bonding)^{16}	1	[74]
$[Fe(\pi\text{-}C_5H_5)(CO)SCH_3]_2^+$	2.93	151°	$+2\frac{1}{2}$	$(XZ_b)^2(Z_b^2)^2(XZ^*)^2(Z^{2*})^2(YZ)^2$ (non-bonding)$^8(YZ^*)^1$	$\frac{1}{2}$	[75]
$[Fe(\pi\text{-}C_5H_5)(CO)SC_6H_5]_2$	3.39	164°	+2	$(XZ_b)^2(Z_b^2)(XZ^*)^2(Z^{2*})^2(YZ)^2$ (non-bonding)$^8(YZ^*)^2$	0	[76]

[a] R = C_2H_5.
[b] S—S distance = 2.01 Å.

2.2. Plant Ferredoxins: 2Fe-2S* Proteins

No crystallographic data are available yet to provide unequivocal information on the structure of the redox centers in two iron—two labile sulfur proteins but there is now much spectroscopic and magnetic evidence for the arrangement shown in Fig. 3, particularly as analyses of the bacterial proteins (see Section 2.3) reveal that the labile sulfur is indeed inorganic sulfide rather than cysteine persulfide.

The bonding scheme formulated[77] for these and other bridged binuclear and polynuclear complexes is summarized in Figure 3. The metal d_{z^2}, d_{xz} and d_{yz} orbitals, the sulfur lone pair orbital, which is essentially directed towards the center of the metal-metal axis, and sulfur filled 'p' orbitals are utilized in bridge bonding; of the remaining metal orbitals, *n* are directed towards the (*n*) terminal ligands and $9-(3+n)$ are assumed to be non-bonding (an adequate description except when strongly π-accepting ligands such as carbon monoxide are present). Use of the theory can be illustrated by a consideration of the complexes $[(\pi C_5H_5)Fe(CO)(SC_6H_5)]_2$ and $[(\pi C_5H_5)Cr(NO)(SC_6H_5)]_2$ where the metal-metal bond lengths are 3.39 Å[78] and 2.95 Å[76] respectively. The electronic configuration of the chromium complex is $(XZ_b)^2(Z_b^2)^2(XZ^*)^2(Z^{2*})^2(YZ)^2$(non bonding)^8 whereas it is $(XZ_b)^2(Z_b^2)^2(XZ^*)^2(Z^{2*})^2(YZ)^2$(non bonding)$^8(YZ^*)^2$ in the iron

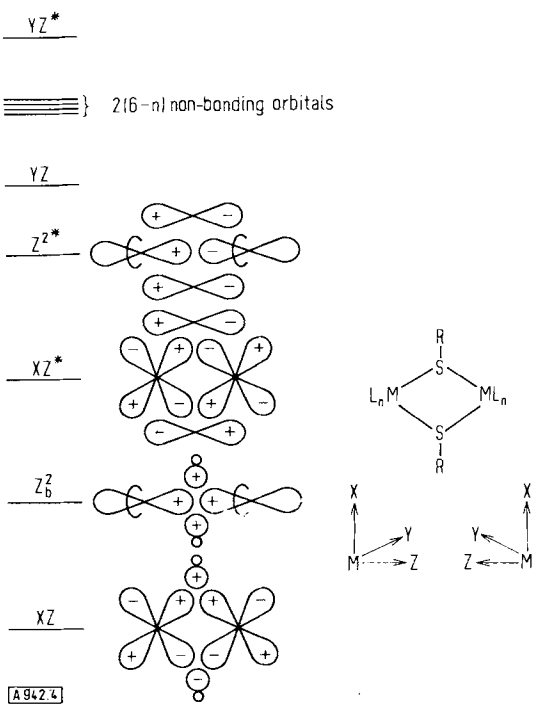


Fig. 4. Schematic representation of the bridge orbitals in sulfur-bridged dimeric species.

complex; thus the metal-metal bond order is approximately unity for the chromium complex and zero for the iron species.

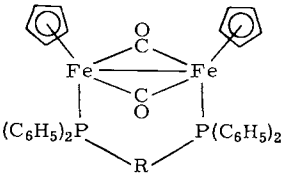
This theory provides also a rationale for the shorter metal-metal bond length in the cationic species $[Fe(\pi C_5H_5)(CO)(SCH_3)]_2^+$ where the YZ* orbital, which is antibonding with respect to the metals, is populated by one electron, compared to the neutral binuclear species in which this orbital is doubly filled. In the case of those complexes with unit bond order, the variation in metal-metal distances reflects the Lewis acidity of the terminal ligands, that is, their ability to accept electron density from those bridge orbitals which are antibonding with respect to the metal-metal bond.

The changes in the metal-metal distances in mercapto-π-cyclopentadienyliron carbonyl and its cation have been interpreted[75] as implying that the geometries of the reduced and oxidized plant ferredoxins differ significantly with respect to the iron-iron distance. However, other workers take the view that the iron-sulfur chromophore geometry remains invariant during the redox process as a result of the steric constraints imposed by the polypeptide chain[79]. Our views on the redox-induced changes are based on the schematic molecular orbital scheme of Figure 3 and an inspection of the variation of metal-metal distances and bridge geometries of Table 2. There is a correlation between the non-planarity of the bridges in the iron-sulfur bridged dimers and the metal-metal distances. For metal-metal distances in the vicinity of the iron covalent diameter (*ca.* 2.5 to 2.6 Å), interelectron repulsions are very sensitive to further reduction of the bond length. The energy of the system will be reduced on bending the Fe_2S_2 framework across the S—S line. As the Fe_2S_2 ring becomes increasingly non-planar, the energies of the bonding orbitals XZ and Z^2 will change only slowly, those orbitals involving the sulfur p_z orbital will change more dramatically; the orbitals XZ*, Z^{2*} and YZ* become less anti-bonding in character. The usual postulate of bent metal-metal bonds in these complexes reflects, in molecular orbital language, a structural change which lowers the total energy of the system; our argument is entirely similar to that established for simpler molecules by *Walsh* and other workers[80].

All the binuclear systems discussed above contain iron in the low spin state, whereas in the plant ferredoxins it is high spin. This fact alone must result in an increase in the covalent radius of about 0.1 Å. The bonding scheme (Fig. 4) indicates that in the reduced state of the plant chromophore the iron-iron bond order is at least one, the (YZ*) antibonding orbital being unfilled. One could suggest therefore a metal-metal distance of about 2.7 Å in the case of coupled high spin ions. Oxidation would remove an electron from the XZ* or Z^{2*} orbital (the relative ordering of these is not known), the net result of which will be a shortening of the metal-metal bond by *ca.* 0.15 Å together with a development of non-planarity in the bridge. That at least would follow from results on model systems. The major qualification that must be made is that bending of the bridge is a very low energy distortion—it could be enhanced or prevented by the steric requirements of the protein chain[*].

The spectroscopic data on the chloroplast ferredoxins all point to a certain degree of charge localization on one iron center following reduction, that is to an Fe^{2+}/Fe^{3+} system. Further studies by *Phillips*[83] on the contact shifts of cysteine protons in a variety of reduced plant ferredoxins shows that the environment about the reduced (ferrous) iron remains invariant whereas that about the ferric iron differs from species to species. It is reasonable to anticipate that the coordination geometry about the 'ferrous' iron is more nearly planar than tetrahedral.

Only one series of complexes is known to us which bears directly on the argument concerning the possibility of bridge conformational changes upon redox reactions in the Fe_2S_2 ferredoxins and a resultant non-equivalence of the iron atoms in the reduced plant proteins: the molecules $[\{(\pi\text{-}C_5H_5)Fe(CO)\}_2(C_6H_5)_2PRP(C_6H_5)_2]$ and their monocations (see Table 3).



[*] Many other dimers of the type $(MX)_2$ containing a variety of transition metals and bridging ligands (X = S, N or O) are known, and have been discussed elsewhere [67, 81]. Variations in M—M bond lengths can be related to the electronegativity of the bridging groups, a fact reflecting the contribution of the 'p' orbitals on the bridging ligands to the bridge molecular orbitals. The qualitative correlation noted earlier between the Fe—Fe bond length and dihedral angle in sulfur bridged binuclear species is not a general one. *Dessy* [82] has recently calculated activation parameters for a series of phosphido-bridged iron dimers and found that inversion of the Fe_2P_2 system is characterized by an activation enthalpy of only 2.2 kcal/mol. Steric effects may contribute significantly to the stabilization of a particular conformer in the case of amido- and phosphido-bridged compounds.

Table 3. Mossbauer data for the series $[\{(\pi\text{-}C_5H_5)Fe(CO)\}_2(C_6H_5)_2\text{-}PRP(C_6H_5)_2]^n$, $n=0, 1+$.

—R—	Chemical isomer shift	Quadrupole splitting Δ [mm s^{-1}]
neutral complexes		
$-CH_2-$	0.30 ± 0.01	1.84
$-N(C_2H_5)-$	0.29 ± 0.01	1.89
$-CH_2-CH_2-$	0.31 ± 0.01	1.88
cations		
$-CH_2-$	0.28	1.98
$-N(C_2H_5)-$	0.28	1.77
$-CH_2-CH_2-$	0.30	1.70

These cations have room temperature magnetic moments corresponding to one unpaired electron per two Fe atoms. Mossbauer studies indicate that the two iron atoms are non-equivalent, suggesting charge localization, that is an Fe^{2+}/Fe^{3+} system as exists in reduced ferredoxin (Table 3).

Not unexpectedly, in view of the difference of the ligands in these complexes and in reduced ferredoxin, the absolute values of the Mossbauer parameters are quite different: for oxidized ferredoxin $\delta=0.25$, $\Delta=0.60$; while in the reduced ferredoxin these values are 1.29 and 2.18 mm s^{-1} respectively. The significant point is the suggestion that non-equivalence of the iron atoms can be produced by low-energy deformations of the bridge geometry in these binuclear complexes. For the neutral complex, a metal-metal bond order of unity is predicted from our earlier theory—not an unlikely presumption on the basis of the iron-iron distance of 2.60 Å in the analogous $[(\pi\text{-}C_5H_5)Fe(CO)_2]_2$ complex[84]. The (YZ*) antibonding orbital is unpopulated, but oxidation again results in the removal of an electron from the Z^2* or XZ* antibonding orbitals. The resulting cationic species should have a shorter metal-metal bond length and a non-planar bridge. This is in keeping with the IR data; the carbonyl stretching frequencies suggest that the bridge is non-planar in the complexes $[\{(\pi\text{-}C_5H_5)Fe(CO)\}_2(C_6H_5)_2PRP(C_6H_5)_2]^+X^-$, the deviation from planarity, based only on the ratio of the A_1 and B_1 mode intensities following the series $R = -N(C_2H_5)- \ll -(CH_2)_2- < -CH_2- < -(CH_2)_3- < -CH=CH-$. This trend parallels the relative rates of oxidation of the derivatives by iodine and $Ag^{\oplus}$.

One final general point should be made concerning the redox behavior of binuclear complexes. The presence of metal-metal bonds correlates well with the ability to yield stable radical anions although many species undergo irreversible two-electron reductions. *Vlček* points out[85] that a negative redox potential can be expected for high spin systems, and assumes that the greater the similarity in the electronic and atomic configuration of the two forms of the redox system, the higher the rate of electrode reaction: in cases where the internuclear distances change considerably, the redox process must have a relatively high activation energy. This offers some support to the views we have developed above for ferredoxins, that redox changes involving Fe^{2+}/Fe^{3+} dimeric systems may be accompanied by bridge angular deformations and that the values of the redox potential may be very sensitive to the capacity of the system to undergo low energy distortions which in turn will reflect its overall stereochemical freedom.

2.3. Polynuclear Iron-Ferredoxins: $Fe_4S_4^*$ and $Fe_8S_8^*$ Systems

Several models for the chromophores in these proteins have been postulated. Recent X-ray analyses of the high potential proteins from *Chromatium* and of ferredoxin from *P. aerogenes* have established that the iron and labile sulfur atoms are arranged in a 'cubane' cluster, the first coordination sphere of the iron atoms being completed by cysteine-sulfurs (Fig. 5). Structural parameters for the biological clusters and related iron-sulfur cubane complexes are collected in Table 4.

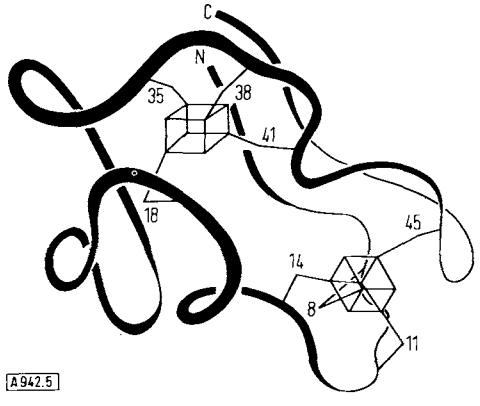


Fig. 5. Course of the main chain of ferredoxin (*P. aerogenes*) (after *Jensen*, 1972; see Ref. [64]).

Only one eight-iron protein has been analyzed completely but there are several lines of evidence pointing to the arrangement in *P. aerogenes* being representative of all the bacterial ferredoxins. The possibility of two separated clusters was recognized by crystallographic studies[7] on ferredoxin (*C. acidi-urici*) and by dithionite titration-reduction as monitored by the EPR spectra of two ferredoxins[93, 101]. The established homologies in the amino acid sequences of several bacterial ferredoxins[43], particularly in and around the eight cysteine residues, argue for closely related structures.

In ferredoxin from *P. aerogenes*, the two iron-sulfur chromophores are separated by 12 Å (Fig. 5). Each cubane cluster is surrounded by hydrophobic residues (Ile, Val, Pro, Gly); unlike structural expectations based on the sequence of cysteine residues, a cross-over of cysteine ligands occurs so that the terminal cysteine sulfur atoms of cluster 1 belong to residues 8, 11, 14 and 45, cluster 2 being formed from cysteine residues 18, 35, 38 and 41.

As discussed in Section 3, of particular significance are the two tyrosine residues, 28 and 2, which are arranged parallel to an Fe—S—Fe—S face of each cluster and separated by an average distance of 3.5—4.0 Å[64]. There is an invariance of aromatic amino acid residues at these positions in the sequences of all bacterial ferredoxins and their implication in the electron transfer process was hinted at earlier by observations of the loss of characteristic EPR and electronic absorption spectra of the ferredoxin on

Table 4. Structural parameters of biological clusters and related cubane-form iron-sulfur complexes.

	Fe--Fe	Fe—S	Symmetrry	No of Fe--Fe Bonds/Iron	Ref.
$[FeS(\pi\text{-}C_5H_5)]_4$	2.65 [a] 3.37 [c]	2.22 [b]	D_{2d}	1	[86, 87]
$[FeS(S_2C_4F_6)]_4^{2-}$	2.80 2.80 2.78 2.58 3.19 3.26	2.22 (inorg) 2.21 (ligand)	D_{2d}	2	[88]
Chromatium HIPIP					
Oxidized	2.73	2.26 (inorg) 2.20 (cysteine)	$\approx T_d$	3	[89]
Reduced	2.81	2.32 (inorg) 2.22 (cysteine)	$\approx T_d$	3	
Ferredoxin *(P. aerogenes)*	2.8	2.3	$\approx T_d$	3	[64]
$[FeS(SCH_2C_6H_5)]_4^{2-}$	2.75	2.29 (inorg) 2.25 (thiolate)	$\approx T_d$ [d]	3	[90]
$[Fe(CO)(\pi\text{-}C_5H_5)]_4$	2.52		T_d	3	[91]
$[Fe(CO)(\pi\text{-}C_5H_5)]_4^+$	2.48		D_{2d}	3	[92]

[a] Average of 2.
[b] Average.
[c] Average of 4.
[d] Small D_{2d} distortion.

acetylation of the tyrosine hydroxyl groups[94] and by changes in the ORD-CD spectra around 250 nm on reduction[95]. The overall conformation of the molecule is such that it possesses a fairly good two-fold rotation axis of symmetry.

The structural parameters of Table 4 can be rationalized in a fairly straightforward way which allows a definite view to be taken of the structural consequences of one-electron redox processes in the biological chromophores. The D_{2d} symmetry of $[(\pi\text{-}C_5H_5)FeS]_4$, with only one Fe—Fe bond per iron atom[86, 87], is consistent with an eighteen electron configuration around each iron (the π-C_5H_5 anion is assumed to be a six electron donor to the (formal) ferric ion (d^5); six electrons are donated to the irons by the sulfur atoms, the remaining one electron being used for the formation of one metal-metal bond per iron). For four-electron donor terminal ligands, such as the substituted alkene-1,2-dithiol tetranuclear complexes of *Balch*[96], two essentially equivalent metal-metal bonds per iron are to be expected. These complexes are, however, different in one important respect from the remaining tetranuclear species; the alkene-1,2-dithiol ligand is a powerful Lewis acid so that one or two electron reduction of the complex must leave its geometry essentially invariant, the added electrons being largely associated with the ligands. A nice demonstration of this lies in the magnetic circular dichroism (MCD) spectra of $[(\pi\text{-}C_5H_5)FeS]_4$, $[(CF_3CS)_2FeS]_4$, ferredoxin *(M. lactilyticus)* and their monoanions (Figure 6); the MCD spectra of the π-cyclopentadienyl complex and ferredoxin change on reduction; this establishes localization of the electron on the cluster in these two cases.

The thiolate-containing and biological clusters are much more symmetrical. This is to be anticipated: For a cluster

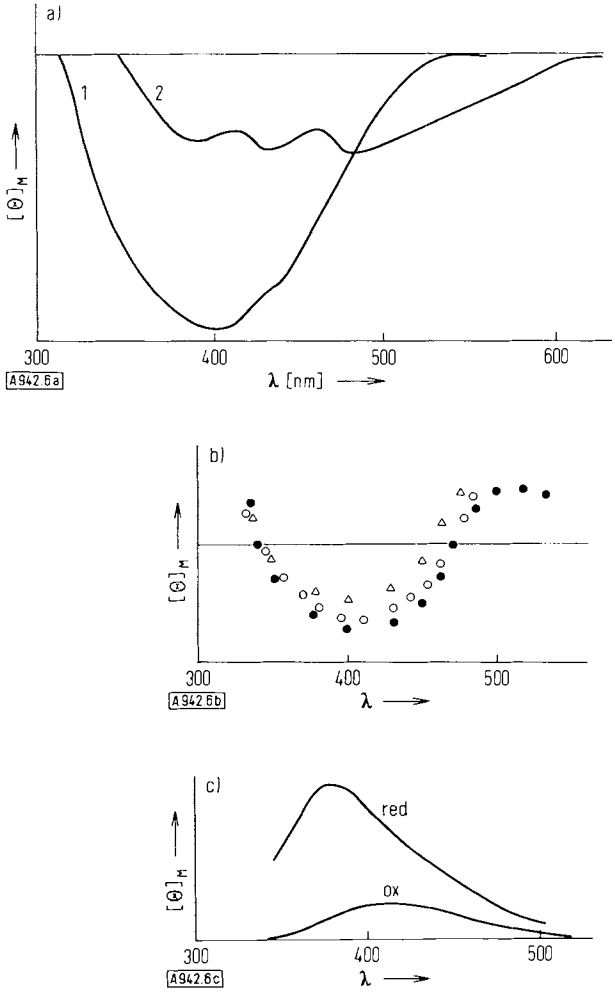


Fig. 6. MCD spectra of iron-sulfur complexes. a) 1: $[(\pi\text{-}C_5H_5)FeS]_4$; 2: $[(\pi\text{-}C_5H_5)FeS]_4^+$. b) $[(CF_3CS)_2FeS]_4^n$; △: $n=0$; ●: $n=1-$; ○: $n=2-$. c) oxidized (ox) and reduced (red) ferredoxin *(M. lactilyticus)*.

of zero net charge, the two electron donor terminal ligands and bridging sulfides provide a sixteen electron configuration around each (formal) ferric ion having three metal-metal bonds per iron. Reduction of these clusters will not change their geometries to any significant extent, the added electrons going to orbitals which are not strongly antibonding with respect to metal-metal bonds (one has still not reached, even in the case of the dianion, an effective 18 electron configuration for the metal).

3. Some Remarks and Speculations on Electron Transfer Processes in Metalloproteins

The available structural results on iron-sulfur proteins and cytochrome c proteins are beginning to pose some interesting problems and questions:

1. How does the $[RSFeS]_4$ cluster cover a range in redox potential of nearly 1 volt?

2. Given that the $[RSFeS]_4$ unit can accept up to two electrons, why have two one-electron transfers to separate clusters in the eight-iron proteins?

3. How is the function of a redox protein related to its total conformation?

4. Why does Nature require a range of iron-sulfur proteins based on mononuclear, binuclear and tetranuclear chromophores?

The range in redox potential of 0.7 V between the high potential protein and the bacterial ferredoxins implies that Nature discovered an effective ligand system for both di- and trivalent iron when sophisticated alternatives (heme) were unavailable. Three groups of redox systems involving iron-based chromophores may be delineated: cytochrome c_3, flavoproteins and iron-sulfur proteins with potentials around -0.3 V; flavoproteins, iron-sulfur proteins and cytochrome b with potentials around 0.0 V; and cytochrome c_1, c and a and copper- and iron-sulfur proteins with potentials up to $+0.25$ V. The electron transfer chain involves movement from one group to another through electron transfer components of alternating redox potential; moreover, potentials must be adjusted to those of the acceptor and donor groups—but in what manner?

The essential structural identity of the redox centers in HIPIP and ferredoxin makes, at first sight, an answer to the first question very difficult. But the difficulty really relates to the question as to whether the redox processes in HIPIP and ferredoxin are equivalent. There seems to be fairly conclusive evidence, particularly from magnetic susceptibility and magnetic resonance data[90], for the following oxidation state equivalences in the clusters:

$$[(C_6H_5CH_2S)FeS]_4^{2-} \equiv [\text{Reduced HIPIP}(Fe_4S_4)] \equiv [\text{Oxidized Fd}(Fe_4S_4)]$$

That the natural oxidation states of the biological clusters differ by one or two units must be related, presumably, to variations in the incidence of acidic and basic residues in and around the active site and hence to the overall protein makeup. The positive redox potential in HIPIP and the potential of -0.5 V in ferredoxin refer to electron transfer to clusters of quite different electronic configuration and are not comparable in any sense. The positive potential of the HIPIP protein is, of course, suggestive that, in so far as it is useful to talk about formal oxidation states, the iron is in the ferrous state; ESCA measurements appear to confirm this and also that ferric iron is present in oxidized ferredoxin[97].

Three separate points need to be made on the general observation that multi-electron transfer in enzymes or enzyme systems appears to require the appropriate number of one-electron acceptor chromophores (probably six Fe_4S_4 clusters in the case of nitrogenase as is discussed later). The first is the obvious truism—that the electron affinity of the monoanion cluster will be very low; the redox processes[90]

$$[C_6H_5CH_2SFeS]_4^{1-} \xleftarrow[-0.2\,V]{} [C_6H_5CH_2SFeS]_4^{2-} \underset{-1.2\,V}{\rightleftharpoons} [C_6H_5CH_2SFeS]^{3-}$$

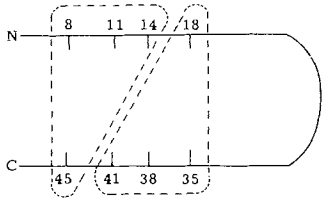
are well illustrative of this fact. The necessity for the biological system to operate around the hydrogen electrode potential implies that two-electron acceptor chromophores would have to exist naturally in a strongly oxidized state.

Secondly, and more importantly, we need to return to the question of the mechanism of the electron transfer and concomitant structural changes. The detailed X-ray analyses of oxidized and reduced cytochrome c by *Dickerson et al.*[98] demonstrate the remarkably general structural implications of one electron transfer reactions in so far as residues very far removed from the heme site change their conformation considerably. Of particular interest is the observation that the tyrosine residue—which sits over the redox center in the oxidized protein—is removed from any obvious interaction with it in the reduced enzyme. There are aromatic residues in close contact with the chromophores in both rubredoxin and ferredoxin and their role can be imagined to be one of 'one-electron trap-doors'. In oxidized ferredoxin, the interplanar separation between the tyrosine residues and a face of the tetranuclear cluster is *ca.* 3.5 Å; one would not necessarily postulate a strong charge-transfer contribution to the ground state non-valence interactions between these atoms. The aromatic residues may readily form radical anions—they are more generally exposed to the surface of the protein compared with the clusters which are located in hydrophobic pockets. The strong Lewis basicity of the aromatic radical anion coupled with good overlap of its antibonding orbital with a cluster orbital could obviously lead to facile one-electron transfer from the aromatic to the inorganic chromophore. Further electron transfer to one cluster is prevented by general conformational changes[*].

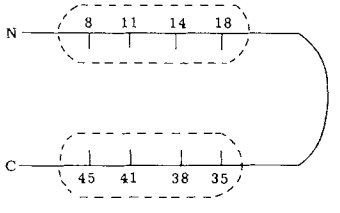
[*] *Note added in proof:* We have overlooked pulse radiolysis experiments which, *inter alia*, implicate aromatic amino acid residues as sites of transient radical intermediates in the reactions of OH radicals and e_{aq}^- with enzymes and metalloproteins [*e.g. N. N. Lichtin, J. Ogden*, and *G. Stein*, Biochim. Biophys. Acta *276*, 124 (1972); *M. Faraggi* and *I. Pecht*, J. Biol. Chem. (in press)]. RM is grateful to Professor *Stein* and Dr. *Pecht* for bringing these results to his attention. More directly ^{13}C magnetic resonance studies of the tyrosyl residues of ferredoxin (*C. acidi-urici*) implicate them in the electron transfer process [*E. L. Packer, H. Steinlicht*, and *J. C. Rabinowitz*, Proc. Nat. Acad. Sci. *69*, 3278 (1972)] although these authors imagine that the radical anion is produced by electron transfer *from* the iron-sulfur cluster. This suggestion may not be consistent with the MCD data of Figure 6.

We have previously emphasized the essential constancy of the tetranuclear cluster geometry to one-electron transfers; but this assertion now needs closer examination. Simple electron counting predicts, as we have seen, symmetrical clusters for $[RSFeS]_4^n$ and for the simple complexes, $[C_6H_5CH_2SFeS]_4^{n-}$ ($n=0,1,2$). But the thiolate cluster dianion has a small D_{2d} distortion. The simple rationale of the small distortion is to assume that in a regular cluster with equivalent metal-metal bonds, the highest lying energy level is orbitally degenerate and that the molecule is therefore subjected to the first order Jahn-Teller effect. A similar proposal has been made by *Frisch* and *Dahl* to explain the C_{2v} distortion of $[(\pi\text{-}C_5H_5)_3Co_3S_2]^+$ from the D_{3h} geometry of the uncharged Co_3S_2 fragment[99]. Thus redox coupled changes of the iron-iron bond lengths in the tetranuclear clusters ranging up to 0.1 Å or so can be anticipated and, as in cytochrome c, considerable overall conformational changes in the protein may result.

In this connection, it should be noted that on anaerobic reduction titration of the eight-iron ferredoxins, two different EPR signals arise which suggest two somewhat different paramagnetic sites—the redox properties of one cluster are connected with the oxidation state of the other although direct electron-electron interaction is surely unlikely. One may speculate that the need to have general allosteric changes in the protein following one-electron transfers is the reason for the crossover arrangement, A, rather than the sequential structure, B. Intuitively, structural changes would be more localized in the sequential structure and, functionally, the protein becomes less adaptable and flexible.



A



B

It will be of considerable interest to discover whether, as one might predict, crossover occurs in the four iron—four labile sulfur—six cysteine sulfur proteins. Here, as was mentioned earlier, the protein chain is a hybrid of the bacterial and plant protein sequences. The plant proteins have five cysteine residues and one may ask why they do not have a corresponding tetranuclear redox center? The much larger and more sophisticated plant protein chain must have evolved in response to such requirements as incorporation in membranes and lamellae; it can be imagined that the particular positioning of the cysteine residues is determined by criteria other than their potential for the formation of a tetranuclear cluster and that the binuclear structure is adequate over a more limited redox range.

4. Other Iron-Sulfur Proteins

Two enzyme systems are worthy of final mention. The structure and function of xanthine oxidase has been reviewed recently[54]; steric and functional interrelationships between the molybdenum-containing chromophores, the flavin groups and the iron-sulfur centers will become clear only through a complete structural analysis. That is just feasible whereas the characterization of the enzyme complex known as nitrogenase is only just beginning.

Apart from certain surfaces of transition metals, nitrogenase is probably the most versatile catalyst, reducing substrates as various as dinitrogen to protons. Nitrogenase from *C. pasteurianum*, *A. vinelandii*, and *K. pneumoniae* are identical in being made from two proteins (known variously as fraction I and fraction II; molybdoferredoxin and azoferredoxin; azofermo and azofer). The first has a molecular weight of 200,000—250,000 and contains 1—2 molybdenum atoms and *ca.* 20 iron and labile sulfur atoms; the second has a molecular weight of approximately 65,000 (two electrophoretically identical sub-units) with four iron and labile sulfur atoms (Table 1). The ESR spectrum of the smaller protein is very similar to those of the plant ferredoxins, the obvious implication being that each subunit has a binuclear chromophore rather than the four irons being arranged in a tetranuclear cluster.

There are sufficient biological analogs for the plausible suggestion that the two proteins are redox coupled in some way. It is attractive also to suggest that the 20—24 iron—labile sulfur atoms in molybdoferredoxin are in six tetranuclear clusters and to correlate this speculation with the six-electron reduction of nitrogen to ammonia[100]. But the basic premise of these speculations needs emphasis—it is that one could have simultaneous transfer of six electrons to the substrate from what must be considerably separated chromophores (the presently available evidence on the mechanism of biological nitrogen fixation is that it is a concerted process). Our view is that the correlation (if it exists) is coincidental; binuclear iron-sulfur chromophores in molybdoferredoxin cannot be excluded at this point. The structural implications of electron transfer in enzymes have been discussed earlier; a plausible speculation for nitrogenase would be that six-electron transfer to molybdoferredoxin is required to produce the overall conformation necessary for activity but that it is not necessary to envisage subsequent concerted electron transfer from the separated chromophores to the substrate. In this model electrons from solvent molecules would be conveyed to the molybdenum-iron reducing center *via* intervening aromatic residues in an entirely equivalent way to that which has been discussed for the cytochrome and ferredoxin proteins. This suggestion can be posed as a general question, "What is the evidence that electron-transfer enzymes actually transfer electrons to a substrate which is being reduced?" At present, the evidence is negligible if not non-existent.

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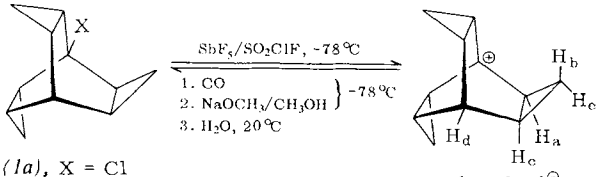
COMMUNICATIONS

Stabilized Bridgehead Carbenium Ions: 1-Trishomobarrelyl and 1-Trishomobullvalyl Cations[**]

By *Armin de Meijere* and *Otto Schallner*[*]

Bridgehead carbenium ions which, due to ring strain, cannot assume the favored planar configuration are as a rule considerably destabilized compared to *tert*-alkyl carbenium ions[1]. Correspondingly, bridgehead halides of bicyclo[2.2.2]octane solvolyze at least 10^7 times more slowly than *tert*-butyl halides[2], but in contrast 1-chlorotrishomobarrelene and 1-chlorotrishomobullvalene react more than 10^2 and 10^4 times, respectively, faster than *tert*-butyl chloride[3]. Thus it was to be expected that in superacid media[4,5] the free carbenium ions of the latter systems should be stable and spectroscopically detectable.

If a cooled solution of SbF_5 in SO_2ClF is added with stirring to a suspension of 1-chlorotrishomobarrelene *(1a)* in SO_2ClF at -78 °C, a clear solution is formed whose ^{1}H-NMR spectrum shows four groups of lines for deshielded protons at $\delta = 2.34$ (q/3 H_c), 3.14 (q/3 H_c + H_d), 3.47 (q/3 H_b), and 3.72 ppm (q/3 H_a). In view of the number, intensity, and coupling of these NMR signals the solution contains

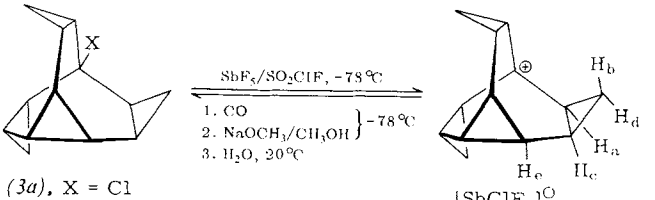


(1a), X = Cl
(1b), X = CO_2H
(1c), X = OCH_3

(2)

the free 1-trishomobarrelyl cation *(2)*. This solution can be warmed in the spectrometer stepwise to -10 °C without change in the spectrum; only at 0 °C does slow polymerization of the cation *(2)* set in. If, as a first step, carbon monoxide is fed into the solution of *(2)* at -78 °C, and the solution is then added dropwise to a cooled methanolic sodium methoxide solution and finally treated with water, 1-trishomobarrelenecarboxylic acid *(1b)*[6] and 1-methoxytrishomobarrelene *(1c)*[6] can be isolated in 53% and 24% yield, respectively.

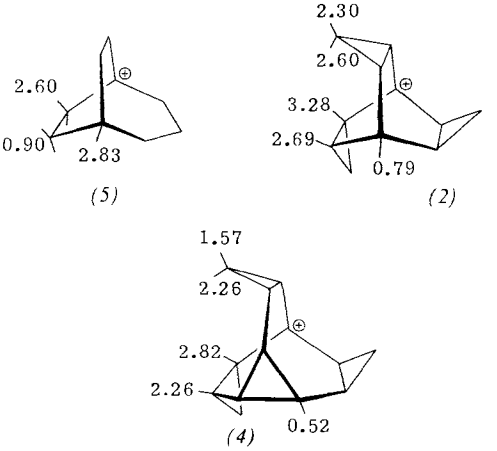
The free cation *(4)* can be generated from 1-chlorotrishomobullvalene *(3a)* analogously to *(2)*. In this case the ^{1}H-NMR spectrum contains signals at $\delta = 1.66$ (broad s/3 H_c), 2.09 (broad s/3 H_d), 3.18 (2 broad s/3 H_b + 3 H_c), and 3.58 ppm (m/3 H_a). The solution of *(4)* is stable only up to -40 C; polymerization sets in at -30 C even after a few minutes.



(3a), X = Cl
(3b), X = CO_2H
(3c), X = OCH_3

(4)

The ion *(4)* can also be trapped without rearrangement; under the same conditions as for *(2)*, 1-trishomobullva-



(5) *(2)* *(4)*

Fig. 1. Differences ($\Delta\delta$) between the chemical shifts in some bridgehead carbenium ions (δ_{cation}) and in the corresponding parent hydrocarbons (δ_{HC}). The $\Delta\delta$-values of *(5)* are referred to 1-methoxybicyclo[3.2.2]nonane [5].

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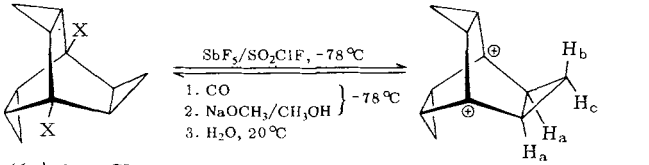
lenecarboxylic acid *(3b)*[6] and 1-methoxytrishomobullvalene *(3c)*[6] are formed in 9% and 65% yield, respectively.

The NMR signals of *(2)* and *(4)* are assigned by comparison of the spectra with those of the hydrocarbons trishomobarrelene and trishomobullvalene[7,8] and of a series of bridgehead derivatives of these systems[3,8]. On comparing the NMR data for *(2)* and *(4)* with those of the 1-bicyclo[3.2.2]nonyl cation *(5)* which has recently been investigated[5], one notices two important differences (cf. Fig. 1). The deshielding of the bridgehead proton in *(2)* and of the three "skeletal" cyclopropyl protons in *(4)* is appreciably less than that of the bridgehead proton in *(5)*. In contrast, all the "wing" cyclopropyl protons in *(2)* and *(4)* are relatively strongly deshielded, whereas in *(5)* the protons in the β-position to the carbenium ion center are notably less deshielded than those in the α-position. *Olah et al.*[5] have attributed the strong deshielding of the bridgehead proton in *(5)* to a charge delocalization which can take place on the one hand through the C—C σ-bond orbitals arranged parallel to the bridgehead p-orbitals and on the other hand directly through space ("cage effect"). It is readily understood that because of the more rigid geometry of *(2)* the distance between the two bridgehead C atoms is larger than for *(5)* and thus the charge delocalization through space is smaller for *(2)*. Apparently, in *(2)* and *(4)* the charge delocalization transmitted through the cyclopropyl-C—C bonding orbitals on to the opposite bridgehead must also be considerably less than that through the C—C σ bonds in *(5)*. The cyclopropane rings in the α-position to the carbenium ion center in *(2)* and *(4)* act, as a whole, so well as electron-donors that the positive charge is delocalized approximately equally on to all the centers of these "wing" cyclopropane rings[9].

The surprisingly high stability of *(2)* led us to treat 1,5-dichlorotrishomobarrelene *(6a)*[11] with SbF_5 in SO_2ClF at −78 °C. A smooth reaction occurred affording a clear solution whose ^{1}H-NMR spectrum showed three groups of lines at δ = 2.55 (q/3H_c), 3.41 (q/3H_b), and 3.75 ppm



(6a), X = Cl
(6b), X = CO_2H
(6c), X = OCH_3

2 $[SbClF_5]^{\ominus}$

(7)

(t/6H_a). Double resonance measurements revealed that upon irradiation at δ = 2.55 ppm the signals at 3.41 and 3.75 were simplified to a triplet and a doublet, respectively. The solution can be warmed stepwise to 0 °C without change in the NMR spectrum[12].

In view of these findings the solution might contain the 1,5-trishomobarrelyl dication *(7)*, which would be stabilized both thermodynamically and kinetically by the "wing" cyclopropane rings in the α-position to the carbenium ion centers, exactly as in *(2)*. Supporting chemical evidence was obtained, as for *(2)* and *(4)*, by trapping with carbon monoxide and sodium methoxide in methanol; 1,5-trishomobarrelenedicarboxylic acid *(6b)*[6] and 1,5-dimethoxytrishomobarrelene *(6c)*[6] were isolated in 74% and 5% yield, respectively.

However, the ^{1}H-NMR spectroscopic and chemical observations would also be consistent with the presence of a 5-chlorotrishomobarrelyl monocation in which the chlorine substituent undergoes a rapid intermolecular exchange reaction[14].

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[9] This is in accord with results of theoretical studies [10], according to which the cyclopropane ring strongly interacts with a neighboring positive center but can only weakly transmit the conjugation effect further.

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[11] *(6a)* was obtained as a by-product on photochlorination of trishomobarrelene with *tert*-butyl hypochlorite; if a two-fold excess of *tert*-butyl hypochlorite is used, *(6a)* becomes the main product [8].

[12] In contrast, the 1-bicyclo[3.2.2]nonyl cation rearranges rapidly at −60 °C [5] and the 1-bicyclo[2.2.2]octyl cation even at −78 °C [13].

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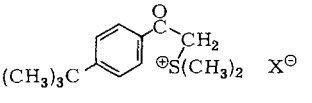
[14] Preliminary ^{13}C-NMR spectroscopic data indicate that in solution there exists a temperature dependent equilibrium between three cationic species, probably a monocation-monochloride, a monocation-monochloride-SbF_5 complex and the dication *(7)*.—Dr. *G. D. Mateescu*, Case Western Reserve University, Cleveland, Ohio (USA), has called our attention to the fact that he recently characterized the congressane dication [cf. Diss. Abstr. Int. *B 32*, 3223 (1971); Chem. Abstr. *76*, 98566f (1972)].

The Tetraphenylborate Ion as NMR-Shift Reagent for Sulfonium Compounds[1]

By *Günter Paulus Schiemenz* and *Hans Peter Hansen*[*]

Sulfonium salts such as *(1a)* and *(1b)* associate in only slightly polar solvents to short-lived contact ion pairs in which the charge centers are as close together as possible.



(1a), X = Br
(1b), X = $B(C_6H_5)_4$

If $B(C_6H_5)_4^-$ is the counter-ion then protons, particularly those in the α-position to the onium center, take up positions *above* one of the benzene rings of the anion; their NMR signals are thus strongly "shielded"[2]. The S—CH_3 signal of *(1b)* in CD_2Cl_2 is shifted upfield by 1.8 ppm with respect to the bromide *(1a)*, and the S—CH_2—CO— signal by 3.1 ppm (cf. Table 1). In the less polar solvent $CDCl_3$ the effects are even more pronounced, especially for S—CH_3 (2.3 and 3.3 ppm upfield shift respectively).

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Table 1. ^{1}H-NMR data for sulfonium salts *(1)*.

	δ in CD_2Cl_2 [ppm] [a]				δ in $CDCl_3$ [ppm] [a]			
	Concn. [b]	S—CH_3	S—CH_2CO	C—CH_3	Concn. [b]	S—CH_3	S—CH_2CO	C—CH_3
(1a) [c]	0.068	3.355	6.270	1.340	0.080	3.480	6.180	1.315
(1b) [d]	0.071	1.595	3.190	1.350	0.034	1.190	2.865	1.340
(1a)/*(1b)* *ca.* 1:1	0.069	2.240	4.325	1.350				

[a] Instrument: Varian A-60; relative to $(CH_3)_4Si$ as internal standard.
[b] Mol of salt per kg of solvent.
[c] From *p-tert*-butylphenacyl bromide and dimethyl sulfide in benzene at room temperature; m.p. 120—121 °C.
[d] Almost quantitative precipitation from equimolar aqueous solutions of *(1a)* and $Na[B(C_6H_5)_4]$; m.p. 156 °C.

The $(CH_3)_3C$-protons, however, no longer lie *above* the benzene ring but with free rotation around the C—C_{arom} bond approach to within a minimum distance from them approximately *in* the plane of the ring. Thus, as with *p-tert*-butylbenzylammonium salts[1, 3], these signals suffer a *slight downfield* shift; here too the anion effect is greater in $CDCl_3$ than in CD_2Cl_2 (cf. Table 1).

Mixtures of *(1a)* and *(1b)* show complete averaging. So, by choice of the appropriate concentrations, the signals can be shifted, without broadening, to any desired position within the limits set by the pure salts. $B(C_6H_5)_4^-$ is thus an effective nuclear magnetic resonance shift reagent for sulfonium cations.

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[1] Ions, Part 9.—Part 8: *G. P. Schiemenz*, Tetrahedron, *29*, 741 (1973).

[2] For this expression see *P. Hamm* and *W. von Philipsborn*, Helv. Chim. Acta *54*, 2363 (1971).

[3] *G. P. Schiemenz*, Org. Magn. Resonance, in press; J. Mol. Struct., in press.

Conversion of Vicinal Diols into Dicarbonyl Compounds by Manganese Dioxide

By *Günther Ohloff* and *Wolfgang Giersch*[*]

Methods for oxidative cleavage of vicinal diols have considerable preparative interest[1]. We here report a new procedure for almost quantitative fragmentation of these compounds in the heterogeneous phase under extremely mild conditions. We have found that treating 1,2-diols of varying degrees of substitution with an excess of activated MnO_2[2] and CH_2Cl_2 affords dicarbonyl fragments at room temperature[3].

As Table 1 shows, only 1,2-*cis*-diols and analogous *trans*-compounds with a flexible arrangement of their hydroxyl groups undergo this new type of fragmentation. Even diols subject to extensive sterical hindrance give the expected fragments quite smoothly (see the last example in Table 1). On the other hand, 9,10-*trans*-decalindiol[4] remains inert even if the reaction time is considerably prolonged.

If the hydroxyl groups are secondary, dehydrogenation is observed in isolated cases instead of complete fragmentation. For example, dodecanedial[5], as a fragmentation product of 1,2-*cis*-cyclododecanediol[6] is accompanied by 14% of 1,2-cyclododecanedione[7] and traces of 2-hydroxycyclododecanone[8].

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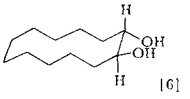
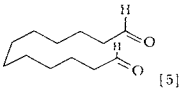
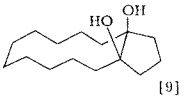
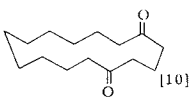
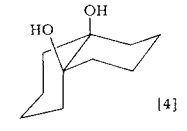
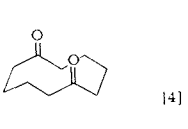
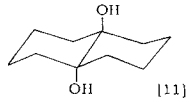
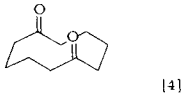
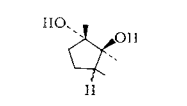
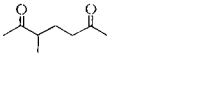
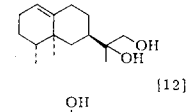
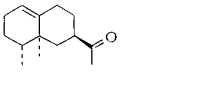
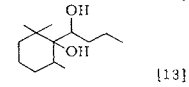
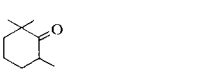
Table 1. Products of oxidation of 1,2-diols by manganese dioxide.

Starting material	Product	Time [h]	Conversion [%]	Yield [%]
 [6]	 [5]	4	100	85
 [9]	 [10]	2	100	70
 [4]	 [4]	1	100	90
 [11]	 [4]	72	0	
		5	100	70
 [12]		1	100	60
 [13]		2	100	90

Experimental

9,10-*cis*-Decalindiol (1 g)[4] is stirred in CH_2Cl_2 (50 ml) with activated MnO_2 (20 g)[2] at room temperature. Thin-layer chromatographic analysis showed the diol to have reacted completely after 1 h. The MnO_2 was then filtered off on Celite, the solvent was removed at water-pump vacuum in a rotary evaporator, and the residue was distilled, affording 1,6-cyclodecanedione, m.p. 92—95 °C (from acetone) (0.9 g, 90%)[4]. The spectral data for gas-chromatographically pure dione accord with those of the authentic product[4].

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[8] *W. Ziegenbein*, Chem. Ber. *94*, 2989 (1961).

[9] Obtained from the corresponding allylic alcohol by successive conversion into the hydroperoxide *(7)* (as designated in [10]), treatment with peracetic acid, and reduction of the resultant α,β-hydroxyperoxide by LiAlH

[10] *G. Ohloff*, *J. Becker*, and *K. H. Schulte-Elte*, Helv. Chim. Acta *50*, 705 (1967).

[11] *W. Hückel*, *R. Danneel*, *A. Schwartz*, and *A. Gercke*, Liebigs Ann. Chem. *474*, 121 (1929).

[12] Obtained by treatment of (+)-valencene with $Pb(OAc)_4$ in benzene at 65 C [14] and subsequent hydrolysis of the diacetate.

[13] Obtained by complete catalytic hydrogenation (Raney nickel/methanol) of a mixture of compounds *(3a)* and *(4a)* (as designated in [15]).

[14] *R. Criegee*, Angew. Chem. *70*, 173 (1958).

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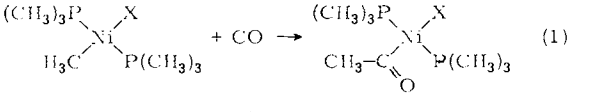
Acetylnickel Halides by Insertion of CO into Ni—C σ-Bonds

By *Hans-Friedrich Klein*[*]

The insertion of carbon monoxide into the nickel-carbon bond of an intermediate is seen as the main principle in many catalytic reactions[1]. However there has hitherto been no proof of such a step since acetylnickel compounds could not be isolated as intermediates in these processes.

We have found that solutions of methylnickel halide complexes[2] with sterically undemanding trimethylphosphane ligands absorb CO even at normal pressure.



(1)

(1), X = Cl: golden-yellow needles, m.p. 98–99 °C

(2), X = Br: orange-yellow needles decomp. > 88 °C

(3), X = I; brick-red crystals, decomp. > 95 °C

The bis(trimethylphosphane)acetylnickel halides thus formed in smooth reactions (in pentane at 20 °C; quantitative yield) can be isolated in crystalline form and show considerable thermal stability compared with other acetyl derivatives of transition metals[3]. Decarbonylation, by reversal of eq. (1), occurs only to a limited extent, even under drastic conditions: *(1)* can even be transported *in vacuo* (80 °C, 0.1 torr).

The IR spectra of all three complexes contain a very strong, broad C=O stretching vibration band (1635—1650 cm^{-1}) of the acetyl group attached to the nickel. In the region of the Ni—C stretching vibration there are strong bands at 538 *(1)*, 537 *(2)*, and 530 cm^{-1} *(3)*.

The ^{1}H-NMR spectra become deceptively simple at 30 °C owing to rapid ligand exchange: the resonances of the PCH_3 and $COCH_3$ protons appear as singlets with relative areas 6:1; only at low temperature does one observe the PCH_3 resonance as a pseudotriplet, which is typical of the $H_9PP'H_9'$ spin system of *trans*-trimethylphosphane ligands. Under these conditions (5% in CH_2Cl_2, −40 °C) the $COCH_3$ protons appear as triplet ($^4_{cis}J(PH) = 1.4$—1.7 Hz) owing to long-range coupling with two equivalent ^{31}P nuclei. Therefore the products of the CO insertion reaction also adopt a *trans*-square-planar structure in solution. A mode of reaction has thus been realized for nickel that has been known for quite a long time for organo-palladium and -platinum complexes[4].

The only evidence that this CO insertion reaction is reversible is supplied by the reaction of *(1)* with tetrakis(trimethylphosphane)nickel(0) in the course of which a CO ligand is actually mobilized from the acetylnickel group:

$$L_2Ni(COCH_3)Cl + L_4Ni \rightarrow L_2Ni(CH_3)Cl + L_3NiCO + L \qquad (2)$$
$$L = (CH_3)_3P$$

This CO enters as superior ligand into the Ni^0 system in place of a phosphane ligand which in turn is taken up as additional ligand by the methylnickel complex[2].

It is thus not surprising that in the oxidative addition of acetyl chloride to $[(CH_3)_3P]_4Ni$[5], with its complicated course, the complexes expected from eq. (2) are found experimentally as the main products.

It is thus now clear why decarbonylation always occurs in the oxidative addition of acyl halides to phosphane-substituted Ni^0 compounds[6], whereas the acyl stage can be observed only with Ni^0 complexes containing the CO-like isocyanide ligands[7].

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Transannular π-π Interaction in Cyclophanes[1]

By *Roberto Boschi* and *Werner Schmidt*[*]

Cyclophanes are distinguished by unusual physical and chemical properties whose origin has been the subject of lively discussion in the last two decades[2]. Three qualitative models—π electron repulsion between the benzene units[3], hyperconjugation with the bridging CC bonds[4], and nonplanarity of the benzene rings[5]—have been

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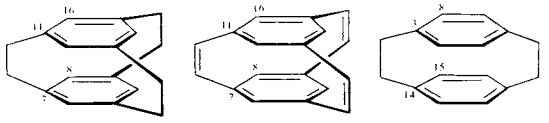
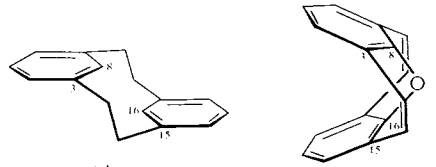
employed to rationalize these effects. In order to discriminate between these alternatives, we have determined the interaction of the benzene e_{1g} orbitals in the highly strained cyclophanes *(1)*—*(5)* by photoelectron (PE) spectroscopy.



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



(4) *(5)*

Table 1. Vertical ionization energies *IE* and energy differences ΔIE between the s and a components of the benzene e_{1g} levels [6] in [2.2.2](1,3,5)cyclophane *(1)*, [2.2.2](1,3,5)cyclophane-1,9,17-triene *(2)*, [2.2]paracyclophane *(3)*, [2.2]metacyclophane *(4)*, and 8,16-oxido-*cis*[2.2]metacyclophane-1,9-diene *(5)*.

Compound	*IE* (eV)	ΔIE_s	ΔIE_a
(1), D_{3h}	7.70 e″ 8.75 e′	1.05	1.05
(2), D_{3h}	8.06 e″ 9.24 e′	1.18	1.18
(3), D_{2h}	8.08 b_{3g} ≈8.6 b_{2g} ≈8.6 b_{2u} 9.53 b_{3u}	0.5	0.9
(4), C_{2h}	8.24 b_u 8.44 a_u 8.75 b_g 9.25 a_g	1.01	−0.3
(5), C_{2v}	7.95 b_2 8.62 b_1? 8.84 a_1? 9.45 a_2	0.2	1.50

Ionization energies *IE* as obtained from the PE spectra are given in Table 1. ΔIE_s denotes the energy difference between the out-of-phase and the in-phase linear combination of the e_{1g}(s) orbitals; ΔIE_a refers accordingly to the e_{1g}(a) components.

$$e_{1g}(s) = 1/2\sqrt{3}(2\varphi_1 + \varphi_2 - \varphi_3 - 2\varphi_4 - \varphi_5 + \varphi_6)$$
$$e_{1g}(a) = 1/2(\varphi_2 + \varphi_3 - \varphi_5 - \varphi_6)$$

For symmetry reasons, both splittings are identical in *(1)* and *(2)*.

The strong transannular interaction, which is expressed in the ΔIE_s and ΔIE_a data, is surprising in view of the relatively large intramolecular distances between the benzene rings: only in *(5)* is this distance considerably smaller than the sum of the Van der Waals radii.

The ΔIE splittings found for *(3)* and *(4)* exceed earlier estimates[3], which were based on UV data, by nearly one power of ten. It should be noted at this point that the direct transannular π-π interaction of the e_{1g} orbitals is partly compensated, in the case of the e_{1g}(a) components of *(4)* even over-compensated, due to the admixture of occupied σ levels of the CC bridges. The ΔIE values in *(1)* and *(2)* are even larger than those in *(3)* and *(4)*; the former pair must consequently be classified as the most strained compounds of the series.

Of greater relevance than the ΔIE splittings are the individual π-π resonance integrals which can be deduced from the ionization energies with the aid of a simple ZDO model[11]. As can be seen from Table 2, they correlate

Table 2. Resonance integrals, $\beta_{\mu\nu}$, of the transannular interaction, and interatomic distances, $R_{\mu\nu}$.

Compound	Centers	$\beta_{\mu\nu}$(eV)	$R_{\mu\nu}$(Å)
(1)	7,11 8,16	−1.6	—
(2)	7,11 8,16	−1.5	2.80 [7]
(3)	3,14 8,15	−1.5 −0.9	2.778 [8] 3.093
(4)	8,16 3,15	−3.2 −0.1	2.69 [9] 3.02
(5)	8,16 3,15	−2.3 ≈0	2.113 [10] 3.075

well with the intermolecular distances and the relative orientation of the interacting π-AOs; *i.e.*, the greater the σ-type overlap at a given distance, the greater is $\beta_{\mu\nu}$.

Whereas π electron delocalization in *(1)*—*(3)* extends over the carbon atoms of *both* benzene units, it is confined in *(4)* and *(5)* to C-8 and C-16; the absolute value of the resonance integral corresponds to that of a normal aromatic π bond. This finding provides the basis for an understanding of the tendency toward transannular ring closure which is commonplace in [2.2]metacyclophane chemistry. Thus, in *(4)* even the mild conditions of electrophilic substitution (or of irradiation in the presence of I_2, or reduction[12] with K) are sufficient to effect elimination of the intra-annular hydrogen atoms to give the 4,5,9,10-tetrahydropyrene system. In the case of *(5)* either oxygen expulsion and subsequent aromatization to pyrene (CF_3COOH/30 °C; benzene/214 °C) occurs, or a 1,3 shift of the oxygen atom affords 1-pyrenol (CH_3OH/123 °C)[13].

Moreover, it may be concluded from the present data that the unusual molecular geometries[7–10] of cyclophanes (distortion of the benzene rings, extremely short H···H contacts) are a consequence, rather than the origin, of the transannular π-π interaction.

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[1] PE spectra of delocalized π systems, Part 10. – Part 9: *R. Boschi, E. Clar*, and *W. Schmidt*, J. C. S. Faraday II, in press.

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[6] Only bands due to ionization from e_{1g} levels are listed. For a detailed discussion of the PE spectrum of *(2)* see: *V. Boekelheide* and *W. Schmidt*, Chem. Phys. Lett. *17*, 410 (1972). We are indebted to Prof. *V. Boekelheide*,

University of Oregon (USA), for a gift of *(1)*, *(2)*, and *(5)*. The PE spectra were recorded on a Perkin-Elmer PS-18 instrument.

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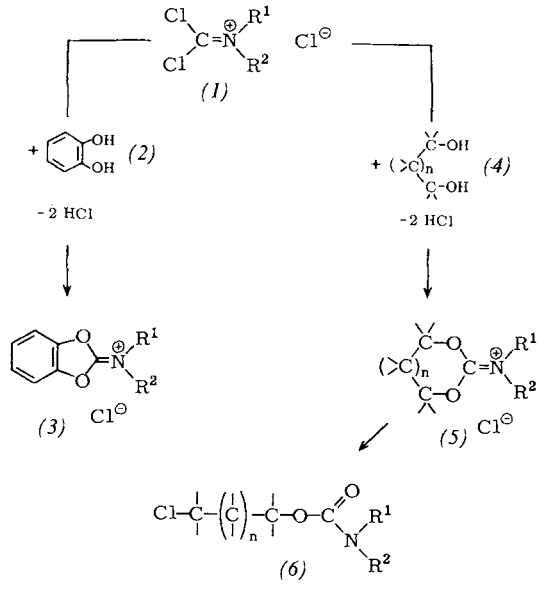
Synthesis of Chloroalkyl Carbamates from Diols and Phosgeneimmonium Salts[1]

By *Brigitte Le Clef, Jacques Mommaerts, Bernard Stelander*, and *Heinz Günter Viehe*[*]

(Dichloromethylene)ammonium chloride (phosgeneimmonium chloride) *(1)* condenses with *o*-dihydroxybenzene *(2)* to give the 1,3-benzodioxol-2-ylideneammonium chlorides *(3)*[2]. Aliphatic diols *(4)* have now been found to undergo a similar reaction giving chloroalkyl carbamates *(6)* *via* the thermally unstable immonium chloride *(5)*. Generally high yields are obtained for symmetrical 1,2-; 1,3-; and 1,4-diols (Table 1). Chloroalkyl carbamates were previously accessible only by multistep syntheses with phosgene, isocyanates, or carbamoyl halides[4-6].

The reaction of pinacol (2,3-dimethylbutane-2,3-diol) with *(1)* stops at the immonium carbonate *(5)*, which can be isolated as a thermally stable compound. This stability probably arises from steric hindrance to attack by the chloride ion which would lead to ring opening. This concept is well substantiated by the observation that *cis*-cyclohexane-1,2-diol forms the *trans*-chlorocyclohexyl carbamate and that unsymmetric diols preferentially give products resulting from attack by the chloride ion at the least hindered side of the ring in *(5)* (Table 2).



In the presence of HCl, diols react with cyanogen chloride to give chloroalkyl carbamates bearing no substituent on the nitrogen *(6)*, $R^1=R^2=H$[3], and chloroalkyl carbamates having a secondary nitrogen atom *(6)*, $R^2=H$, can be obtained from isocyanide dichlorides and HCl, presumably also *via* an intermediate of type *(5)*[7] (Table 3).

Experimental:

Synthesis of 2-chloroethyl N,N-dimethylcarbamate: 3.1 g (0.05 mol) of glycol is added dropwise at 25 °C to a stirred suspension of *(1)* (8.1 g, 0.05 mol) in dichloromethane solution. Stirring is continued until *(1)* is completely dissolved. The solvent is then evaporated off and the residue is distilled (90 °C/13 torr). 7.5 g (*ca.* 100%) of 2-chloroethyl *N,N*-di-

Table 1. Chloroalkyl *N,N*-dimethylcarbamates R—O—C(=O)—$N(CH_3)_2$ synthesized from dichloromethylene-*N,N*-dimethylammonium chloride *(1)* and symmetric diols.

Diol	Reaction conditions	Carbamate R	Yield (%)	B. p. (°C/torr)	NMR ($CDCl_3$, TMS = 0) δ(ppm)
Ethylene glycol	25 °C	Cl—$(CH_2)_2$— [4]	100	90/13	2.98 (6H, s); 3.74 (2H, t); 4.32 (2H, t)
cis-Cyclohexane-1,2-diol	CH_2Cl_2, 30 min boiling	*trans*-2-Chlorocyclohexyl	92	80/0.5	1.00—2.42 (8H, m); 2.98 (6H, s); 3.60—4.40 (1H, m); 4.38—5.92 (1H, m)
$(CH_3)_2C(CH_2OH)_2$	25 °C	$(CH_3)_2C(CH_2Cl)$—CH_2—	95	102—110/13	1.02 (6H, s); 2.98 (6H, s); 3.36 (2H, s); 4.00 (2H, s)
$CH_2(CH_2OH)_2$	25 °C	Cl—$(CH_2)_3$—	96	100—105/13	2.08 (2H, q); 2.96 (6H, s); 3.64 (2H, t); 4.24 (2H, t)
$CH_2[CH(CH_3)OH]_2$	25 °C	CH_3—CHCl—$CH_2(CH_3)$—	90	100/13	1.22 (3H, d); 1.50 (3H, d); 2.98 (6H, s); 4.18 (1H, m); 5.00 (1H, m)
HO—$(CH_2)_4$—OH	CH_2Cl_2, 30 min boiling	Cl—$(CH_2)_4$—	40	100—102/13	1.58—2.10 (4H, m); 2.98 (6H, s); 3.64 (2H, m); 4.18 (2H, m)

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Table 2. Chloroalkyl *N,N*-dimethylcarbamates R—O—C(=O)—$N(CH_3)_2$ synthesized from dichloromethylene-*N,N*-dimethylammonium chloride *(1)* and unsymmetrical diols at 25 °C.

Diol	Carbamate R	Total yield (%)	Isomer ratio	B. p. (°C/torr)	NMR ($CDCl_3$, TMS = 0) δ (ppm)
C_2H_5—CH(OH)—CH_2OH	C_2H_5—$CH(CH_2Cl)$—	86	90:10	107/17	0.96 (3H, t); 1.70 (2H, q); 2.98 (6H, s); 3.68 (2H, d); 4.82 (1H, q)
	C_2H_5—CHCl—CH_2—				0.96 (3H, t); 1.72 (2H, q); 2.98 (6H, s); 4.22 (3H, m)
CH_3—CH(OH)—$(CH_2)_2$OH	Cl—$(CH_2)_2$—$CH(CH_3)$—	90	82:18	115/20	1.28 (3H, d); 2.05 (2H, q); 2.98 (6H, s); 3.62 (2H, t); 5.02 (1H, q)
	CH_3—CHCl—$(CH_2)_2$—				1.58 (3H, d); 2.05 (2H, q); 2.98 (6H, s); 4.04—4.52 (3H, m)

Table 3. Chloroalkyl *N*-alkylcarbamates R—O—C(=O)—NHR^1 synthesized from alkyl isocyanide dichlorides.

Diol	Reaction conditions	Carbamate R	R^1	Yield (%)	NMR ($CDCl_3$, TMSO = 0) δ (ppm)
Ethylene glycol	25 °C	Cl—$(CH_2)_2$— [5]	CH_3	100	2.87 (3H, s); 3.75 (2H, t); 4.40 (2H, t); 5.17 (1H, m)
$CH_2(CH_2OH)_2$	25 °C	Cl—$(CH_2)_3$— [6]	CH_3	100	2.10 (2H, q); 2.80 (3H, s); 3.66 (2H, t); 4.23 (2H, t); 5.45 (1, m)
$(CH_3)_2C(CH_2OH)_2$	CH_2Cl_2, 15 min boiling	$(CH_3)_2C(CH_2Cl)$—CH_2—	CH_3	95	1.00 (6H, s); 2.70 (3H, s); 3.42 (2H, s); 3.92 (2H, s); 5.47 (1H, m)
Ethylene glycol	CH_2Cl_2, 15 min boiling	Cl—$(CH_2)_2$—	C_6H_{11}	98	1.07—2.17 (10H, m); 3.50 (1H, m); 3.70 (2H, t); 4.33 (2H, t); 5.17 (1H, m)

methylcarbamate is obtained.

Synthesis of 3-chloropropyl N-methylcarbamate: 1.14 g (0.015 mol) of 1,3-propanediol is added dropwise at 25 °C to a stirred solution of 1.70 g (0.015 mol) of methyl isocyanide dichloride saturated with HCl in dichloromethane. Stirring is continued for 30 min. The solvent is evaporated off leaving practically pure 3-chloropropyl *N*-methylcarbamate (2.26 g, *ca.* 100%).

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[1] Immonium Chemistry, Part 7.—Part 6: *Z. Janousek* and *H. G. Viehe*, Angew. Chem. *85*, 90 (1973); Angew. Chem. internat. Edit. *12*, 74 (1973).

[2] *H. G. Viehe* and *Z. Janousek*, Angew. Chem. *83*, 614 (1971); Angew. Chem. internat. Edit. *10*, 573 (1971).

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[4] *A. P. Sineokov* and *G. E. Kholodenko*, Zh. Org. Khim. *4* (9), 1661 (1968).

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Heterocycles from Compounds Containing Two Nucleophilic Centers and Phosgeneimmonium Salts[1]

By *Françoise Hervens* and *Heinz Günter Viehe*[*]

N-(Dichloromethylene)-*N,N*-dimethylammonium chloride ("phosgeneimmonium chloride") *(1)* possesses three very mobile chlorine atoms and is therefore suitable as a starting material for condensation reactions[2–6]. We now wish to report that *(1)* reacts readily with dinucleophiles such as unsymmetrically substituted arylhydrazines *(2)*, amidrazones *(3)*, hydrazides *(4)*, or *o*-phenylene derivatives *(5)* to give high yields of indazoles *(6)*, triazoles *(7)*, oxadiazoles *(8)*, and benzoxazoles *(9)*, X = O, or benzothiazoles *(9)*, X = S. No intermediates have been isolated, although the reaction was followed by NMR spectroscopy until formation of the heterocycles was complete. The structures of the products synthesized were confirmed by NMR, IR, and mass spectrometry.

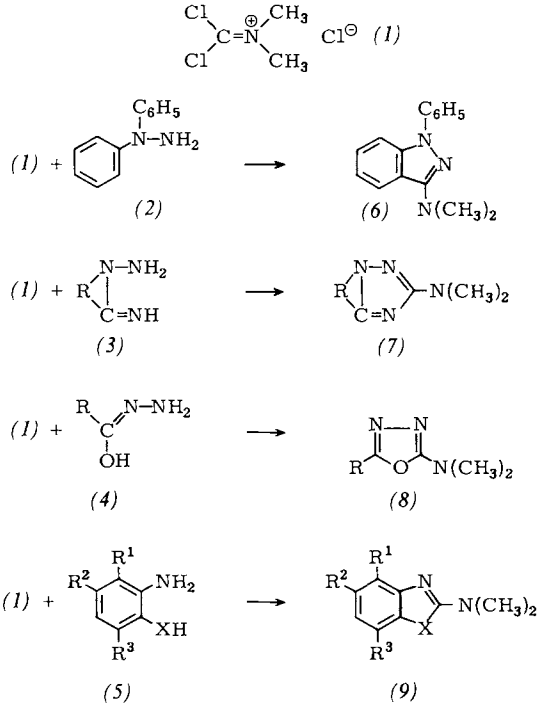

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Table 1. Heterocycles synthesized from *(1)* and dinucleophiles.

Product	Yield (%)	M.p. (°C) b.p. (°C/torr)	NMR ($CDCl_3$, TMS = 0) δ (ppm)
(6)	83	150/0.1	7.4 (9H, m); 3.1 (6H, s)
(7), R = —S—CH=C(CH_3)—	93	70—73	6.35 (1H, s); 3.1 (6H, s); 2.5 (3H, s)
(7), R = —C_6H_4—CH_2—(1,2)	89	106—108	6.8—7.8 (6H, 2m); 3.06 (6H, s)
(8), R = —CH_3	90	100/0.1	2.4 (3H, s); 3.1 (6H, s)
(8), R = —CH_2—C_6H_5	93	75—76	7.3 (5H, s); 4.0 (2H, s); 3.0 (6H, s)
(8), R = 4-pyridyl	95	118—120	3.2 (6H, s); 7.8—8.5 (4H, m)
(9), X = O, $R^1 = R^2 = R^3 = H$	81	90—91	7.3 (4H, m); 3.1 (6H, s)
(9), X = S, $R^1 = R^2 = R^3 = H$ [a]	70	87	7.0 (4H, m); 3.1 (6H, s)
(9), X = O, $R^1 = R^2 = H$, $R^3 = NO_2$	74	164	7.0—8.0 (3H, 2m); 3.16 (6H, s)
(9), X = O, $R^1 = H$, $R^2 = NO_2$, $R^3 = Cl$	71	163	7.8—7.9 (2H, m); 3.2 (6H, s)
(9), X = O, $R^1 = R^2 = R^3 = Cl$	60	139—140	7.03 (1H, s); 3.23 (6H, s)

[a] These compounds have also been synthesized by *K. Nagarajan* and *V. Ranga Rao*, Indian J. Chem. 7, 964 (1969).

Thus phosgeneimmonium salts prove to be at least as useful for the synthesis of heterocycles as the related thioformamide chlorides[7], which suffer from the disadvantage that they can eliminate either HCl or HSR.

Experimental:

Synthesis of (6): 1 mol of *(1)* and 1 mol of *(2)* are boiled under reflux in chloroform for 2 hours until evolution of HCl stops. The solvent is evaporated off and the residue is treated with 2 N KOH and extracted with methylene chloride. The extract is dried over sodium sulfate, the solvent evaporated off, and the residue distilled at 150 °C/0.1 torr.

Synthesis of compounds (7) to (9): 1 mol of *(3)*, *(4)*, or *(5)* and 1 mol of *(1)* are boiled under reflux in chloroform for 1—2 hours until evolution of HCl stops. The solvent is then evaporated off and the residue washed with ether, treated with a solution of 2 N KOH, and then extracted with methylene chloride. The extract is dried over sodium sulfate, filtered, and the solvent finally evaporated off.

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[1] Immonium Chemistry, Part 8.—Part 7: *B. Le Clef, J. Mommaerts, B. Stelander*, and *H. G. Viehe*, Angew. Chem. 85, 445 (1973); Angew. Chem. internat. Edit. 12, 404 (1973).

[2] *Z. Janousek* and *H. G. Viehe*, Angew. Chem. 83, 615 (1971); Angew. Chem. internat. Edit. 10, 574 (1971).

[3] *H. G. Viehe, Z. Janousek*, and *M. A. Deffrenne*, Angew. Chem. 83, 616 (1971); Angew. Chem. internat. Edit. 10, 575 (1971).

[4] *H. G. Viehe, Th. van Vyve*, and *Z. Janousek*, Angew. Chem. 84, 991 (1972); Angew. Chem. internat. Edit. 11, 916 (1972).

[5] *H. G. Viehe* and *Z. Janousek*, Angew. Chem. 83, 614 (1971); Angew. Chem. internat. Edit. 10, 573 (1971).

[6] *Z. Janousek*, Dissertation, Univ. Louvain 1972.

[7] *H. Eilingsfeld* and *L. Möbius*, Chem. Ber. 98, 1293 (1965).

Formation of 1,2,4-Triazolin-5-ones from *tert*-Butylnitroacetylene and Phenylhydrazines[1]

By *Cécile Derycke, Volker Jäger, Jean Paul Putzeys, Maurice Van Meerssche*, and *Heinz Günter Viehe*[*]

Electron-poor nitroacetylenes[2] react with amines and hydrazines to give β-nitroalkenylamines *(2)* and β-nitroalkylidenehydrazines *(3)*, respectively. Surprisingly, however, the reaction of *tert*-butylnitroacetylene *(1)* with phenylhydrazine *(4a)* in ethereal solution at 0 °C gives a new condensation product *(5a)* by loss of water.

The IR spectrum of *(5a)* shows an absorption at 2265 cm^{-1} which is attributed to the —C≡N→O function. *(5a)* can be reduced to the corresponding nitrile *(6a)* by triethyl phosphite in refluxing benzene[3]. On standing for three days at 0 °C, *(5a)* undergoes isomerization, the rate of which can be increased by refluxing in $CHCl_3$. X-Ray analysis shows the isomer to have the structure 3-*tert*-butyl-1-phenyl-1,2,4-triazolin-5-one *(7a)*.

The substituted phenylhydrazines *(4b)* and *(4c)* likewise afford the compounds *(7b)* and *(7c)*.

The nitrile oxides *(5)* and the triazolinones *(7)* can also be obtained from 3,3-dimethyl-2-iodo-1-nitrobutene *(8)* and the phenylhydrazines *(4)* with KOH.

Experimental:

Synthesis of (5a) from (1): Compound *(1)* (258 mg, 2.03 mmol) in ether (5 ml) is added over 5 min with stirring

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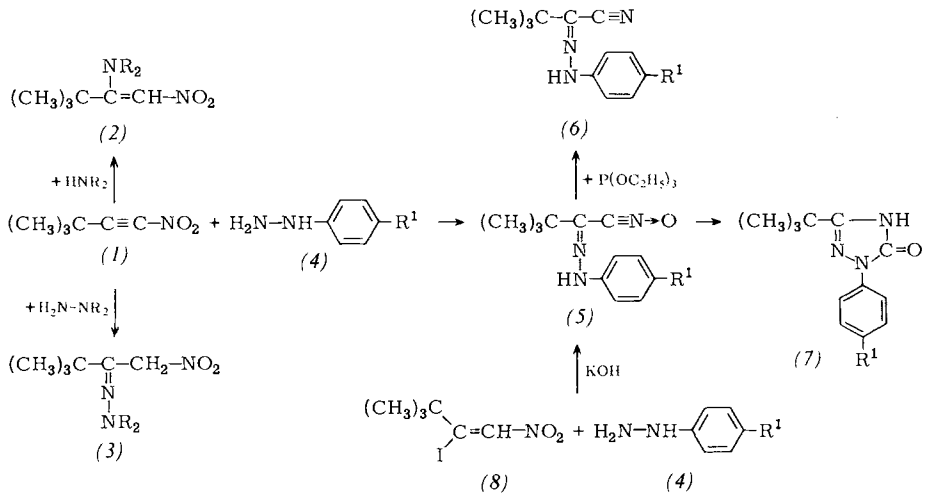

(a), $R^1 = H$
(b), $R^1 = NO_2$
(c), $R^1 = CH_3$

Table 1. Properties of the compounds synthesized.

Product	Yield (%)	M.p. (°C)	IR (cm^{-1})	NMR (TMS=0) δ(ppm)
(5a)	88	86—87	2265	1.25(9H,s); 6.7,7.15(5H,m); 8.22(1H,s)
(6a)	62	59—60	2195	1.25(9H,s); 7.25(5H,m); 8.25(1H,s)
(7a)	71 [a]	209	1690	1.4(9H,s); 7.4,7.9(5H,m); 12.1(1H,s)
(7b)	73 [a]	271	1710	1.4(9H,s); 7.9(4H,s); 11.7(1H,s)
(7c)	87 [a]	220	1685	1.4(9H,s); 2.3(3H,s); 7.15,7.85(4H,m); 12.1(1H,s)

[a] From *(1)* and *(4)*.

to *(4a)* (216 mg, 2 mmol) in ether (5 ml) at 0 °C. The solvent is immediately evaporated off and the residue recrystallized from ether/petroleum ether (b. p. 40—60 °C) to give 385 mg (88%) of *(5a)*.

Synthesis of (7a) from (8): Compound *(8)* (510 mg, 2 mmol) in ether (5 ml) is added with stirring to *(4a)* (216 mg, 2 mmol) in ether (5 ml) and KOH (200 mg) at 0 °C. After the reaction mixture has stood for three days the solvent is evaporated off and compound *(7a)* is obtained by recrystallization of the residue from $CHCl_3$/petroleum ether (b. p. 60—80 °C); yield 91 mg (42%).

Reduction of (5a) to (6a): Triethyl phosphite (665 mg, 4 mmol) is added to *(5a)* (225 mg, 1.04 mmol) in dry benzene (10 ml) over 5 min at room temperature. After 15 minutes' heating on a water bath the mixture is diluted with its own volume of benzene and shaken with 5% H_2SO_4 (20 ml) to decompose excess phosphite. As soon as the characteristic odor of this compound has disappeared the organic layer is washed four times with water and the solvent is evaporated off. The remaining oil is crystallized from ether/pentane to yield 123 mg (62%) of *(6a)*.

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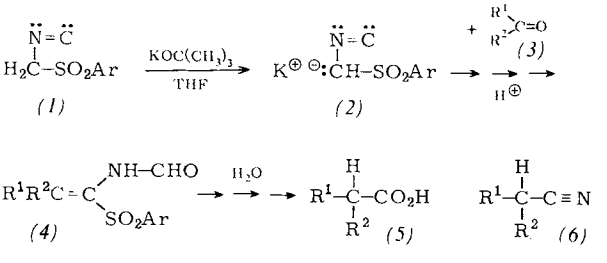
Conversion of a Ketone or an Aldehyde into the Next Higher Nitrile[1]

By *Ulrich Schöllkopf* and *Rolf Schröder*[*]

In a previous communication[2] we described the synthesis of *N*-(1-arenesulfonyl-1-alkenyl)formamides *(4)* from α-metalated arenesulfonylmethyl isocyanides *(2)* and carbonyl compounds *(3)* and their conversion into the next higher carboxylic acid *(5)* by acid or alkaline hydrolysis. The metalated isocyanides were obtained by reaction of arenesulfonylmethyl isocyanides *(1)* with potassium *tert*-butoxide in tetrahydrofuran[2]. At that time we did not engage in a detailed study of the question of which intermediates are involved in the hydrolysis step *(4)*→*(5)*[2]. The observation[3] that 2-cyanoadamantane is formed in the reaction of adamantanone with tosylmethyl isocyanide in ethanol/dimethoxyethane in the presence of sodium ethoxide suggested the intermediacy of the nitriles *(6)* during alkaline hydrolysis and their general accessibility from *(4)*.



This is actually found to be the case. As we have shown (Table 1) the nitriles *(6)* are formed in good yields when *N*-(1-arenesulfonyl-1-alkenyl)formamides *(4)* are refluxed

[1] Nitroacetylenes, Part 4.—Part 3: *V. Jäger* and *H. G. Viehe*, Angew. Chem. *82*, 836 (1970); Angew. Chem. internat. Edit. *9*, 795 (1970).

[2] *V. Jäger* and *H. G. Viehe*, Angew. Chem. *81*, 259 (1969); Angew. Chem. internat. Edit. *8*, 273 (1969).

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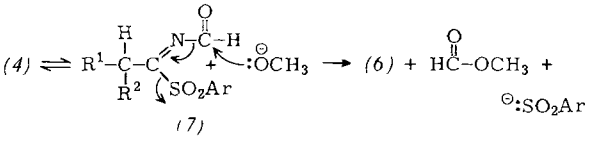
for 15 min with sodium methoxide in methanol. Subject to a detailed study we would tentatively formulate the conversion *(4)*→*(6)* as proceeding *via* the formylimino compounds *(7)* that are tautomeric to *(4)*, their formyl group undergoing nucleophilic displacement from the nitrogen by the methoxide ion with concomitant elimination of an arenesulfinate ion.



(7)

Table 1. Nitriles *(6)* prepared from substituted formamides *(4)*, Ar = *p*-CH_3—C_6H_4.

R^1	R^2	*(6)*	Yield [%]	B. p. [°C/torr]
C_6H_5	H	benzyl cyanide	81	107/12
—$(CH_2)_5$—		cyclohexanecarbonitrile	85	185/760
$(CH_3)_3C$	H	neopentanecarbonitrile	72	135/760
C_6H_5	CH_3	α-methylbenzyl cyanide	69	108/12
CH_3	CH_3	isobutyronitrile	93 [a]	

[a] Crude yield; product identified by gas chromatographic comparison with an authentic sample.

Thus a method is now available for transforming the substituted formamides *(4)*, accessible by "formylaminomethylenation"[2] of carbonyl compounds *(3)*, into either the next higher carboxylic acid *(5)* or the next higher nitrile *(6)* according to choice.

General procedure for the conversion (4)→(6):

A piece of sodium (0.46 g, 20 mmol) is dissolved in methanol (30 ml). *N*-(1-Tosyl-1-alkenyl)formamide *(4)*, Ar = *p*-CH_3—C_6H_4[2], (10 mmol) is added to the resulting gently boiling solution (85 °C bath temperature) and the reaction mixture is refluxed for a further 15 min. After cooling the solvent is removed at 25 °C in a rotary evaporator *in vacuo*. Water (25 ml) is then added and the ethereal solutions obtained on ether extraction (2 × 30 ml) are dried ($MgSO_4$) and worked up in the customary manner. The nitriles *(6)* were distilled (cf. Table 1).

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[1] Syntheses with α-Metalated Isocyanides, Part 25. — Part 24: *U. Schöllkopf* and *K. Hantke*, Liebigs Ann. Chem., in press.

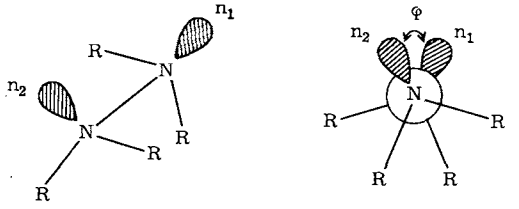
[2] *U. Schöllkopf, R. Schröder*, and *E. Blume*, Liebigs Ann. Chem. *766*, 130 (1972); *U. Schöllkopf* and *R. Schröder*, Angew. Chem. *84*, 289 (1972); Angew. Chem. internat. Edit. *11*, 311 (1972).

[3] Prof. *A. M. van Leusen*, Groningen, personal communication; *O. H. Oldenziel* and *A. M. van Leusen*, Synth. Commun. *2*, 281 (1972).

Photoelectron Spectra and Conformation of Hydrazine Derivatives[1]

By *Paul Rademacher*[*]

Photoelectron (PE) spectroscopy permits quantitative determination of the interaction of molecular orbitals[2]. Since in hydrazine derivatives R_2N—NR_2 the extent of interaction between the two nitrogen lone pairs n_1 and n_2 should vary considerably with the dihedral angle φ between the two halves of the molecule, PE spectroscopy should provide relatively simple access to the conformation of these compounds.



Calculations by the MINDO/2 procedure[3] showed that the energy of the two lone-pair molecular orbitals $E(n_+)$ and $E(n_-)$ varies continuously with φ[4]. Thus at φ = 0° n_- lies 1.45 eV above n_+, at φ = 80° n_- and n_+ have the same energy, and at φ = 180° n_- lies 2.41 eV below n_+. This change of $\Delta E = E(n_-) - E(n_+)$ with φ should be sufficient to determine the dihedral angle from the vertical ionization potentials $I_v(n_+)$ and $I_v(n_-)$ for hydrazine derivatives of different conformations.

By use of *Koopmans'* theorem[5], which states that the orbital energy equals the negative vertical ionization energy, the data in Table 1[6] were obtained in the following way: First, the $\Delta E = f(\varphi)$ curve calculated by the MINDO/2 method was calibrated by means of compounds *(1)*, *(11)*, and *(12)* whose dihedral angles φ were previously known. The value of φ could then be read off from the new curve for each of the molecules listed provided that $I_v(n_+)$ and $I_v(n_-)$ had been assigned in the photoelectron spectra. The assignments were made by MINDO/2 calculations.

Table 1. Vertical ionization potentials (*I*), orbital energy differences (Δ*E*), and dihedral angles (φ) of hydrazine derivatives.

Compound	$I_v(n_-)$ [eV]	$I_v(n_+)$ [eV]	*E* [eV]	φ [°]
Hydrazine *(1)* [7]	10.70	10.02	−0.68	90 [8]
1,2-Dimethylhydrazine *(2)*	9.65	9.02	−0.63	88
Tetramethylhydrazine *(3)*	8.77	8.38	−0.39	79
1,2-Diethylhydrazine *(4)*	9.46	8.88	−0.58	86
1,2-Diisopropylhydrazine *(5)*	9.91	8.34	−1.57	125
Pyrazolidine *(6)*	8.85	7.90	−0.95	101
Piperidazine *(7)*	9.52	8.72	−0.80	95
1,1'-Biaziridine *(8)*	11.18	8.65	−2.53	180
1,1'-Bipiperidine *(9)*	8.37	8.05	−0.32	77
1,5-Diazabicyclo[3.3.0]octane *(10)*	7.90	9.47	+1.57	12
3,4,4,5-Tetramethyl-4*H*-pyrazole *(11)*	10.12	11.93	+1.81	0
Acetaldehyde azine *(12)*	11.63	9.11	−2.52	180

The results for compounds *(2)* to *(4)* show that methyl and ethyl substituents have a negligible influence on the *gauche*-conformation — a finding in agreement with vibrational spectroscopic investigations of *(3)*[9] and electron-diffraction measurements of *(2)*[10], which indicate the *gauche*-conformation for these compounds. In *(5)* the hydrazine skeleton is clearly more twisted by the larger substituents.

The cyclic derivatives *(6)* and *(7)* also exist in the *gauche*-conformation.

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The dihedral angle $\varphi = 180°$ for 1,1'-biaziridine *(8)* agrees with the results of vibrational spectroscopic[11] and electron-diffraction studies[12] which indicated the centrosymmetric *s-trans*-conformation for this molecule. The six-membered ring homolog *(9)*, however, possesses the *gauche*-conformation analogous to the open-chain compounds *(1)* to *(4)*.

In the bicyclic compound *(10)* the repulsion between n_1 and n_2 clearly prevents the molecule from assuming the conformation with minimal ring strain ($\varphi = 0°$), in agreement with IR and Raman spectra of *(10)* which exclude a structure with C_{2v} symmetry.

The results so far with symmetrical compounds suggest that the dihedral angle and thus the conformation of hydrazine derivatives can be determined accurately from the splitting of the two lone-pair molecular orbitals.

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[1] Photoelectron Spectra of Hydrazine Derivatives. Part 1.

[2] See, *e.g.*: *P. Bischof, J. A. Hashmall, E. Heilbronner*, and *V. Hornung*, Helv. Chim. Acta *52*, 1745 (1969); Tetrahedron Lett. *1969*, 4025.

[3] *N. Bodor, M. J. S. Dewar, A. Harget*, and *E. Haselbach*, J. Amer. Chem. Soc. *92*, 3854 (1970).

[4] Here $n_+ = (n_1 + n_2)/\sqrt{2}$ stands for the symmetrical and $n_- = (n_1 - n_2)/\sqrt{2}$ for the antisymmetrical linear combinations of the two semilocalized lone-pair electrons n_1 and n_2.

[5] *T. Koopmans*, Physica *1*, 104 (1934); *W. G. Richards*, Int. J. Mass Spectrom. Ion Phys. *2*, 419 (1969).

[6] The PE spectra were recorded on a Perkin-Elmer PS-16 spectrometer.

[7] A PE spectrum with low resolution was published by *D. W. Turner*: Physical Methods in Advanced Inorganic Chemistry. Interscience Publishers, New York 1968, p. 74.

[8] *T. Kasuya* and *T. Kojima*, J. Phys. Soc. Jap. *18*, 364 (1963).

[9] *D. C. McKean*, Spectrochim. Acta *10*, 1611 (1957).

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[11] *P. Rademacher* and *W. Lüttke*, Angew. Chem. *82*, 258 (1970); Angew. Chem. internat. Edit. *9*, 245 (1970); *P. Rademacher*, Spectrochim. Acta *A 28*, 987 (1972).

[12] *P. Rademacher*, Acta Chem. Scand. *26*, 1981 (1972).

Polymeric Octamolybdate Ions in the Crystal Structure of $(NH_4)_6Mo_8O_{27}\cdot 4H_2O$[**]

By *Irene Böschen, Bruno Buss, Bernt Krebs*, and *Oskar Glemser*[*]

From 0.20—0.25 M aqueous[1] or acidified ammonium heptamolybdate solutions, the latter containing NH_4Cl[2], there separate after about two to three weeks colorless needles of an octamolybdate of the composition $(NH_4)_6Mo_8O_{27}\cdot 4H_2O$. We have now elucidated its structure. The compound forms monoclinic crystals belonging to space group $P2_1/c$ with $a = 9.519 \pm 0.005$, $b = 11.309 \pm 0.006$, $c = 15.049 \pm 0.008$ Å; $\beta = 109.50 \pm 0.03°$, $Z = 2$, $d_{X\text{-ray}} = 3.00$, $d_{exp} = 3.01 \pm 0.02$ g cm^{-3} (cf. [1]).

For the determination of the structure the intensities of 3020 non-equivalent reflections were measured with $Mo_{K\alpha}$ radiation on a Hilger-Watts four-circle diffractometer. The structure could be completely solved by Patterson and Fourier methods. The parameters of all the atoms except H were refined by the method of least squares to an R value of 6.4% (anisotropic temperature factors). The X-ray structure analysis revealed one molecule of water of crystallization per molecule of octamolybdate more than was originally[1] assigned on the basis of analysis.

Figure 1 shows the anion of the structure in an idealized form established in this way. Compact octameric units are linked in each case through a common oxygen atom to give endless chains. The octameric unit is built up of distorted MoO_6 octahedra linked *via* edges and corners, edge sharing predominating in agreement with the structural principles of other isopolymolybdates. Unlike all

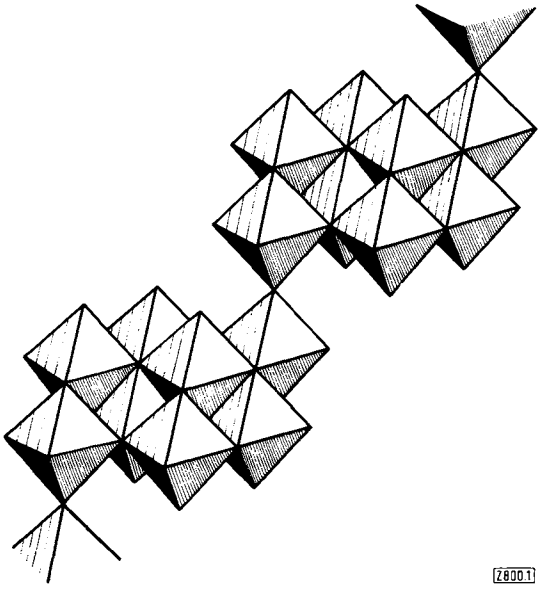

Fig. 1. Polymeric octamolybdate ion $[Mo_8O_{27}]^{6-}$

the other isopolysalts so far known as crystallizing from aqueous solution, the present compound displays polymeric units in its structure. Chain formation was previously observed only for isopolysalts obtained from melts. Interestingly, the octameric unit corresponds in structure to that in the salt $K_2Mo_4O_{13}$ crystallized from melts[3,4]. However, the units in $K_2Mo_4O_{13}$ obtained from melts polymerize *via* shared octahedral edges, whereas the units in $(NH_4)_6Mo_8O_{27}\cdot 4H_2O$ obtained from solution are linked by shared corners.

The Mo—O bond lengths are in the range 1.697 to 2.401 Å with values of 1.697 to 1.732 Å for the terminal bonds. The Mo···Mo distances amount to 3.258 to 3.472 Å for edge linkage and 3.779 to 3.969 Å for corner linkage. The Mo atoms are shifted towards the free corners and edges of the MoO_6 octahedra owing to Mo/Mo Coulomb repulsion and the differing Mo—O bond strengths. In the crystal the anion chains are linked by hydrogen bonds to NH_4^+ ions and water molecules.

Further details of the structure will be reported elsewhere[5].

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[**] This work was supported by the Deutsche Forschungsgemeinschaft.

[1] *O. Glemser, G. Wagner*, and *B. Krebs*, Angew. Chem. *82*, 639 (1970); Angew. Chem. internat. Edit. *9*, 639 (1970).

[2] *W.-D. Humnius*, Dissertation, Freie Universität Berlin 1970.

[3] *B. M. Gatehouse* and *P. Leverett*, Chem. Commun. *1970*, 740.

[4] *B. M. Gatehouse* and *P. Leverett*, J. Chem. Soc. *A 1971*, 2107.

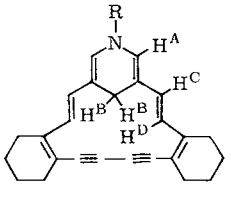
[5] *I. Böschen, B. Buss*, and *B. Krebs*, Acta Crystallogr., in press.

Synthesis of a Methylene-Bridged Didehydroaza[21]annulene, a Diatropic Heteroannulene[1] [***]

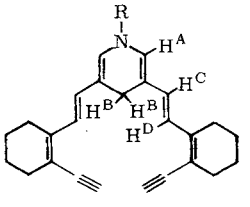
By *Philip J. Beeby* and *Franz Sondheimer*[*]

We have recently described the synthesis of the methylene-bridged didehydroaza[17]annulenes *(1a)*—*(1d)*[2,3]. Comparison of the ^{1}H-NMR spectra of these 18π-electron systems with those of the models *(2a)*—*(2d)* clearly showed the aza[17]annulenes to possess a diamagnetic ring current (=diatropic)[4], these being the first aromatic macrocyclic heteroannulenes of the pyrrole type to be obtained. This type of synthesis appeared to be applicable to the preparation of vinylogous methylene-bridged didehydroaza[19]- and [21]annulenes. These were required in order to discover whether the same alternation of electromagnetic properties between $(4n+2)$ and $4n$ π-electron systems occurs in these heteroannulenes as has already been demonstrated in the carbocyclic annulene series[4]. This synthetic objective has been realized in practice.

The preparation of the methylene-bridged didehydroaza[21]annulene *(7)* is described in the present communication, and that of the corresponding aza[19]annulene in the following one.

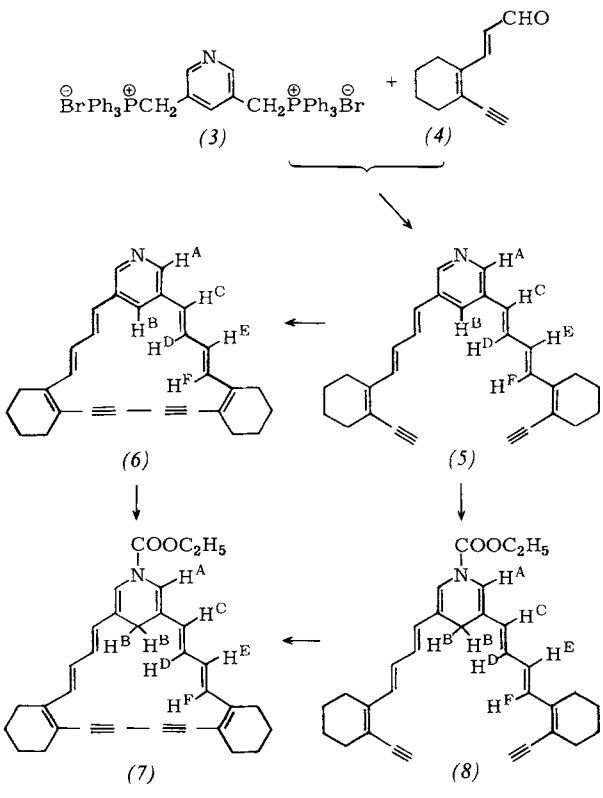


(1a), R = CH_3
(1b), R = H
(1c), R = $COOC_2H_5$
(1d), R = $COCH_3$



(2a), R = CH_3
(2b), R = H
(2c), R = $COOC_2H_5$
(2d), R = $COCH_3$

Wittig reaction of *(3)*[2] and 2 molar equivalents of *(4)*[5] in dimethylformamide with ethanolic lithium ethoxide at 70°C led to *ca.* 65% of the three possible stereoisomeric products, which could not be separated by chromatography. Treatment of the mixture in ether with a small amount



of iodine at room temperature gave a *ca.* 3:1 mixture of the *trans,trans* isomer *(5)* and the corresponding *cis,trans* isomer, which on chromatography on alumina yielded 33% [based on *(3)* and *(4)*] of pure *(5)*[6] as pale yellow crystals; NMR spectrum, see Table 1.

Table 1. ^{1}H-NMR parameters of compounds *(5)*—*(8)* in $CDCl_3$ at 100 MHz (τ values, internal standard TMS) [a].

	Outer H						Inner H		
	H^A	H^C	H^E	allylic H	OCH_2	CH_3	H^B	H^D	H^F
(5) [b]	1.58 d [c]	3.47 d [d]	3.54 dd [e]	7.5—7.9 m	—	—	2.26 t [c]	2.99 dd [e]	2.82 d [d]
(6)	1.74 d [c]	3.43 d [d]	3.53 dd [e]	7.5—7.9 m	—	—	1.48 t [c]	2.78 dd [e]	2.42 d [d]
Δ *(6)*—*(5)*	+0.16	−0.04	−0.01	0.0	—	—	−0.78	−0.21	−0.40
(7) [f]	2.58 s	3.17 d [d]	3.10 dd [e]	7.2—7.6 m	5.61 q [g]	8.60 t [g]	8.00 s	4.61 dd [e]	4.10 d [d]
(8) [h]	3.02 s	3.62 [i]	3.53 [i]	7.5—7.9 m	5.69 q [g]	8.65 t [g]	6.94 s	3.62 [i]	2.95 d [d]
Δ *(7)*—*(8)*	−0.43	−0.45	−0.43	−0.3	−0.08	−0.05	+1.06	+1.00	+1.15
Δ *(1c)*—*(2c)* [j]	−0.64	−0.64	—	−0.35	−0.11	−0.08	+1.86	+1.72	

[a] In addition, all compounds showed a multiplet at *ca.* τ 8.1—8.6 (aliphatic protons).
[b] In addition, *(5)* showed a singlet at τ 6.62 (≡CH).
[c] $J = 2.5$ Hz.
[d] $J = 16$ Hz.
[e] $J = 16$ and 11 Hz.
[f] The assignments of the inner protons were confirmed by nuclear Overhauser experiments.
[g] $J = 7$ Hz.
[h] In addition, *(8)* showed a singlet at τ 6.66 (≡CH).
[i] Degenerate.
[j] At 60 MHz.

Oxidative coupling of the rather unstable *(5)* with cupric acetate in pyridine at 55—60°C resulted in extensive decomposition, and gave only 7%[7] of the cyclic "monomer" *(6)* (orange-red crystals; *m/e* 389). In the NMR

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[***] We are indebted to the Science Research Council for financial support.

spectrum of *(6)*, the "inner" H^B, H^D, and H^F protons have shifted appreciably downfield as compared with *(5)* [Table 1, $\Delta(6)-(5)$]. This is presumably due to the fact that these protons in the relatively rigid macrocyclic structure *(6)* are deshielded by the ethylenic and/or acetylenic bonds to a greater degree than in *(5)*, where free rotation about the single bonds can occur.

Reduction of *(6)* with lithium aluminum hydride in tetrahydrofuran at room temperature led to the corresponding 1,4-dihydropyridine (dark crimson solution), which could not be isolated due to its ready oxidation to *(6)*[8]. The dihydropyridine under nitrogen was therefore treated directly with ethyl chloroformate and pyridine to give 50% of the stable *(7)* as orange-red crystals [*m/e* 463; $\lambda_{max}(CHCl_3)$ 346 (ε 83000), *ca.* 380 sh (37000), *ca.* 406 sh (17000), 429 (16000), 452 (12000), and *ca.* 510 sh nm (2800); NMR spectrum, see Table 1].

Similar reduction of *(5)* with lithium aluminum hydride, followed by treatment with ethyl chloroformate and pyridine, yielded 45% of the model *(8)* as light yellow crystals [$\lambda_{max}(CHCl_3)$ 329 (ε 80000), 339 (85000), 380 (24000), 398 (25000), and *ca.* 424 sh nm (14000); NMR spectrum, see Table 1].

The urethane *(8)* was more stable than the pyridine *(5)*, and its oxidative coupling with cupric acetate in pyridine at 55—60 °C proceeded much better than that of *(5)*. The resulting *(7)*, obtained in 25% yield, proved to be identical with that derived from *(6)*, and this is the preferred route to *(7)*.

Comparison of the NMR spectra of *(7)* and *(8)* [Table 1, $\Delta(7)-(8)$] clearly shows the didehydroaza[21]annulene *(7)* to be diatropic, as expected of a 22 π-electron system, the outer protons being deshielded and the inner protons shielded[9]. This effect is less marked than in the corresponding didehydroaza[17]annulene *(1c)* [Table 1, $\Delta(1c)-(2c)$], showing that diamagnetic ring current effects in $(4n+2)$ π-electron systems become less as the size of the macrocyclic ring is increased.

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[1] Unsaturated macrocyclic compounds, Part 100 — Part 99: *K. Yamamoto* and *F. Sondheimer*, Angew. Chem. *85*, 41 (1973); Angew. Chem. internat. Edit. *12*, 68 (1973).

[2] *P. J. Beeby* and *F. Sondheimer*, J. Amer. Chem. Soc. *94*, 2128 (1972).

[3] See also *P. J. Beeby* and *F. Sondheimer*, Angew. Chem. *84*, 896 (1972); Angew. Chem. internat. Edit. *11*, 833 (1972).

[4] *F. Sondheimer*, Accounts Chem. Res. *5*, 81 (1972).

[5] *R. H. McGirk* and *F. Sondheimer*, Angew. Chem. *84*, 897 (1972); Angew. Chem. internat. Edit. *11*, 834 (1972).

[6] UV, IR, and NMR spectra, as well as elemental analyses, compatible with the assigned structures were obtained for all new compounds. All substances were isolated by chromatography on Woelm neutral alumina (activity III), and consisted of crystals which decomposed on attempted melting point determination.

[7] By comparison, the previously described lower vinylog of *(5)* could be coupled to the corresponding cyclic "monomer" [the precursor of *(1a)—(1d)*] in 85% yield [2].

[8] The corresponding *N*-methyl derivative (dark violet crystals), obtained by successive treatment of the 1,4-dihydropyridine with sodium hydride and methyl iodide, also proved to be quite unstable. The instability of these substances is in contrast to the relative stability of the corresponding derivatives *(1b)* and *(1a)* in the aza[17]annulene series [2].

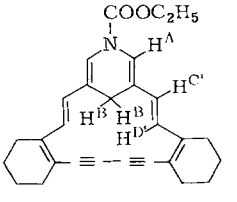
[9] As already discussed for *(1a)—(1d)* [2], the shielding of the inner protons in *(7)* is actually greater than indicated, since the corresponding protons in NMR spectrum of the model *(8)* are at higher field than they would be in the conformation indicated in the formula [see Table 1, $\Delta(6)-(5)$].

Synthesis of a Methylene-Bridged Didehydroaza[19]annulene, a Paratropic Heteroannulene.—The Alternation of Electromagnetic Properties between Hetero[4*n*+1]annulenes and Hetero[4*n*−1]annulenes[1][***]

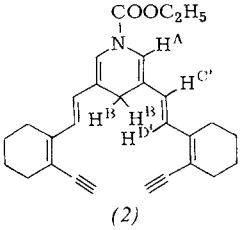
By *Philip J. Beeby* and *Franz Sondheimer*[*]

We have previously reported the synthesis of the methylene-bridged didehydroaza[17]annulene *(1)*[2,3] and didehydroaza[21]annulene *(3)*[1]. Both of these hetero[4*n*+1]annulenes are $(4n+2)$ π-electron systems, and, as expected, comparison of their ^{1}H-NMR spectra with those of the models *(2)* and *(4)* showed them to possess a diamagnetic ring current (= diatropic)[4]. We now describe the synthesis of the methylene-bridged didehydroaza[19]annulene *(19)*, a hetero[4*n*−1]annulene containing $4n$ π-electrons. It was of considerable interest to investigate whether this substance possessed a paramagnetic ring current (= paratropic)[4], a finding which would show that alternation of electromagnetic properties between $(4n+2)$ and $4n$ π-electron systems occurs in these heteroannulenes, as has already been found in the carbocyclic annulene series[4,5].

Reduction of dimethyl pyridine-3,5-dicarboxylate[2] with lithium aluminum hydride in ether, followed by a treatment of the crude 3,5-bis(hydroxymethyl)pyridine[2] with a limited amount of benzoyl chloride in pyridine, gave 30% (based on the diester) of the monobenzoate *(5)* (m.p. 62—63 °C)[6], which was oxidized to the aldehyde *(6)* (m.p. 78—79 °C) in 75% yield with chromium trioxide in pyridine. Reduction of the aldehyde *(7)*[7] with lithium aluminum hydride in ether led to the alcohol *(8)* (liquid), which was converted into the bromide *(9)* (liquid) by means of phosphorus tribromide in ether, and thence to the triphenylphosphonium salt *(10)* [m.p. 240—242 °C (decomp.)] with triphenylphosphane in boiling benzene (overall yield, 85%)[8]. Wittig reaction of *(6)* and *(10)* in dimethylformamide with ethanolic lithium ethoxide at 70 °C (with concomitant hydrolysis of the benzoate group) gave 80% of a *ca.* 1:1 mixture of *(11)* and the correspond-



(1)



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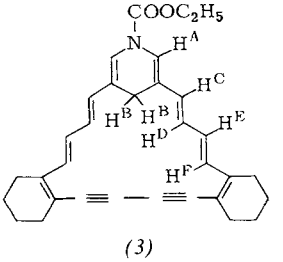

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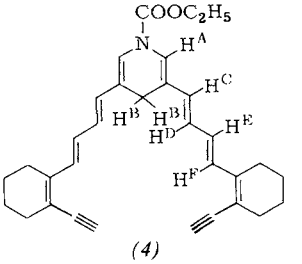

(4)

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[***] We thank the Science Research Council for financial support.

ing *cis* isomer, which was oxidized with manganese dioxide in ether to a *ca.* 1:1 mixture of *(12)* and the corresponding *cis* isomer (48% yield). The stereochemical composition of these mixtures is based on their NMR spectra. Separation by chromatography proved to be difficult, and the synthesis was continued without separation.

The aldehyde *(13)*[9] was transformed to the triphenylphosphonium salt *(16)* (m. p. 170—174 °C) *via* the unstable alcohol *(14)* and bromide *(15)*, in 60% overall yield, by the same route as used for the lower vinylog *(10)*. Wittig reaction of *(12)* (admixed with the corresponding *cis* isomer) and *(16)* in dimethylformamide with ethanolic lithium ethoxide at 70 °C led to *ca.* 80% of the three possible stereoisomeric products, which were difficult to separate. However, careful chromatography on alumina gave material in 25% yield [based on *(16)*], which consisted of *ca.* 75% of the all-*trans* isomer *(17)* as estimated from the NMR spectrum (Table 1).

pure) was converted, through reduction with lithium aluminum hydride and subsequent treatment of the resulting 1,4-dihydropyridine with ethyl chloroformate and pyridine, into the urethane *(18)* [30% yield; yellow crystals which decomposed on attempted melting point determination; *m/e* 439; λ_{max} ($CHCl_3$) *ca.* 300 sh (ε 31000), 315 (51000), 328 (57000), 390 (19000), and *ca.* 414 sh nm (10000); NMR spectrum, see Table 1].

Finally, oxidative coupling of *(18)* with cupric acetate in pyridine at 60 °C gave in 40% yield the aza[19]annulene derivative *(19)* [deep red crystals which decomposed on attempted melting point determination; *m/e* 437; λ_{max} ($CHCl_3$) *ca.* 303 sh (ε 36000), 321 (62000), and 332 nm (65000), with absorption >550 nm; NMR spectrum, see Table 1].

The NMR chemical shift differences for each proton on passing from the model *(18)* to the aza[19]annulene *(19)*

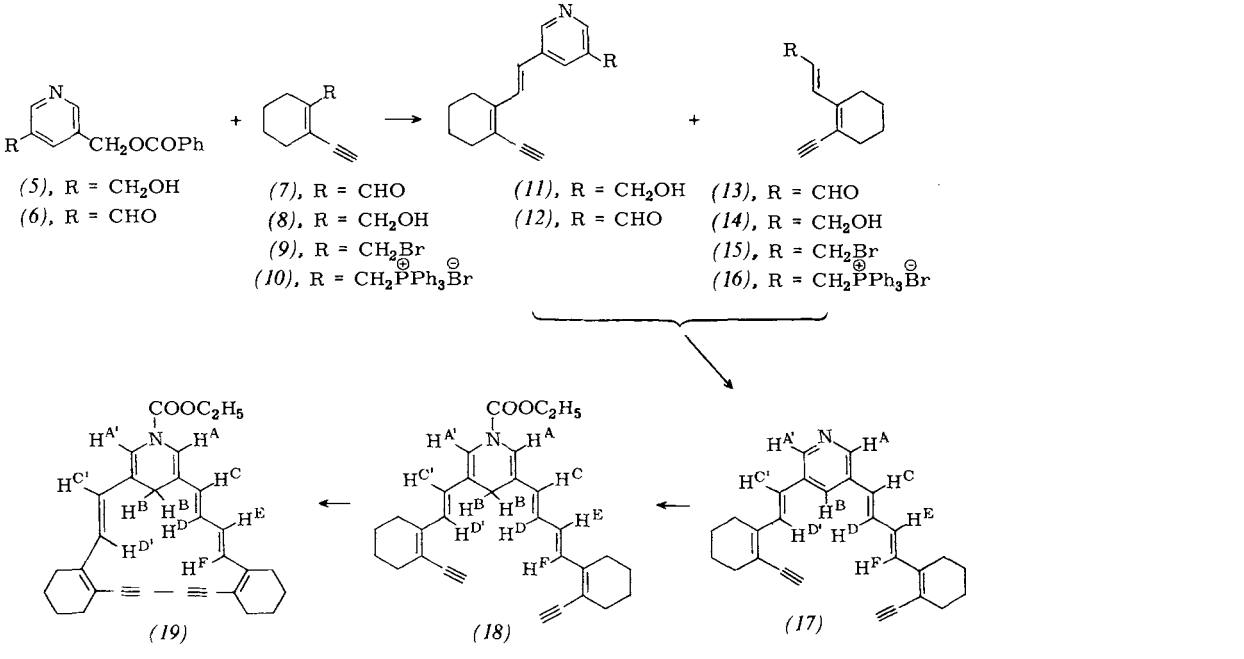
Table 1. ^{1}H-NMR parameters of compounds *(17)*—*(19)* in $CDCl_3$ at 100 MHz (τ values, internal standard TMS) [a].

	Outer H							Inner H			
	$H^A, H^{A'}$	H^C	$H^{C'}$	H^E	allylic H	OCH_2	CH_3	H^B	H^D	$H^{D'}$	H^F
(17) [b]	1.52 d, 1.55 d [c]	3.46 d [d]	3.46 d [d]	3.54 dd [e]	7.5–7.9 m	—	—	2.27 t [c]	2.98 dd [e]	2.38 d [d]	2.86 d [d]
(18) [f]	3.00 s	3.65 [g]	3.58 d [d]	3.55 [g]	7.5–7.9 m	5.70 q [h]	8.65 t [h]	6.93 s	3.65 [g]	3.10 d [d]	2.98 d [d]
(19) [i]	3.42 s	4.10 d [d]	4.00 d [d]	4.05 dd [e]	7.7–8.1 m	5.77 q [h]	8.71 t [h]	5.37 s	1.79 dd [e]	1.20 d [d]	0.86 d [d]
Δ *(19)-(18)*	+0.42	+0.45	+0.42	+0.50	+0.2	+0.07	0.06	−1.56	−1.86	−1.90	−2.12
Δ *(1)-(2)* [j]	−0.64	—	−0.64	—	−0.35	−0.11	−0.08	+1.86	—	+1.72	—
Δ *(3)-(4)*	−0.43	−0.45	—	−0.43	−0.3	−0.08	−0.05	+1.06	+1.00	—	+1.15

[a] In addition, all compounds showed a multiplet at *ca.* τ 8.0—8.6 (aliphatic protons).
[b] In addition, *(17)* showed singlets at τ 6.62 and 6.66 (≡CH).
[c] J = 2.4 Hz.
[d] J = 16 Hz.
[e] J = 16 and 11 Hz.
[f] In addition, *(18)* showed singlets at τ 6.64 and 6.71 (≡CH).
[g] degenerate.
[h] J = 7 Hz.
[i] The assignments of the olefinic protons were established by nuclear Overhauser and decoupling experiments.
[j] At 60 MHz.

Attempts to couple *(17)* to the corresponding cyclic "monomer" with cupric acetate in pyridine were unsuccessful. Advantage of our experience in the aza[21]annulene series[1] was now taken, and the pyridine *(17)* (*ca.* 75%

are given in Table 1 [Δ *(19)—(18)*]. It is evident that the aza[19]annulene *(19)* is paratropic, all the outer protons being shielded and the inner protons deshielded[10] This is a reversal of the behavior of the diatropic



aza[17]annulene *(1)* [Table 1, $\Delta(1)-(2)$] and aza[21]annulene *(3)* [Table 1, $\Delta(3)-(4)$], which are the lower and higher vinylogs of *(19)*, respectively. The alternation of electromagnetic properties between the hetero[$4n+1$]annulenes *(1)* and *(3)* and the hetero-[$4n-1$]annulene *(19)* is thereby clearly established.

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[1] Unsaturated macrocyclic compounds, Part 101.—Part 100: *P. J. Beeby* and *F. Sondheimer*, Angew. Chem. *85*, 404 (1973); Angew. Chem. internat. Edit. *12*, 410 (1973).

[2] *P. J. Beeby* and *F. Sondheimer*, J. Amer. Chem. Soc. *94*, 2128 (1972).

[3] See also *P. J. Beeby* and *F. Sondheimer*, Angew. Chem. *84*, 896 (1972); Angew. Chem. internat. Edit. *11*, 833 (1972).

[4] *F. Sondheimer*, Accounts Chem. Res. *5*, 81 (1972).

[5] The only previously known example of a paratropic heteroannulene is a dioxido-bridged oxa[15]annulene (*H. Ogawa*, *M. Kubo*, and *H. Saikachi*, Tetrahedron Lett. *1971*, 4859). However, the structure of this substance is too different from the diatropic *(1)* and *(3)* to make a meaningful comparison impossible.

[6] UV, IR, and NMR spectra, as well as elemental analyses, compatible with the assigned structures, were obtained for all pure stable compounds.

[7] *P. Schiess* and *H. L. Chia*, Helv. Chim. Acta *53*, 485 (1970); *G. M. Pilling* and *F. Sondheimer*, J. Amer. Chem. Soc. *93*, 1970 (1971).

[8] The transformation of *(7)* to *(10)* (in *ca.* 40% overall yield) was first carried out by Dr. *Gwenda M. Pilling* (Ph. D. Dissertation, Cambridge, 1968; personal communication). The presently reported yield was obtained by Mr. *J. M. Brown* (personal communication).

[9] *R. H. McGirk* and *F. Sondheimer*, Angew. Chem. *84*, 897 (1972); Angew. Chem. internat. Edit. *11*, 834 (1972).

[10] The actual deshielding of the inner protons in *(19)* is presumably smaller (by *ca.* 0.4 ppm) than indicated, since the corresponding protons in the model *(18)* are at higher field than they would be in the conformation indicated in the formula (see reference [1], footnote 9, and reference [2], footnote 9).

μ-Phosphinodiborane

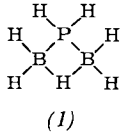
By *Helmut Hofstötter* and *Erwin Mayer*[*]

Although μ-aminodiborane and many of its derivatives substituted on boron or nitrogen have long been known[1], the analogous compounds with phosphorus as bridging element have not yet been described. Pentaborane(9) appears to be the only boron hydride into which phosphorus has hitherto been introduced at a bridging position[2].

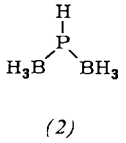
We have found that μ-phosphinodiborane is formed in the reaction of $H_2P(BH_3)_2Na$ with dry HCl in diethyl ether at −96 °C:

$$H_2P(BH_3)_2Na + HCl \rightarrow B_2H_5(PH_2) + NaCl + H_2 \quad (1)$$

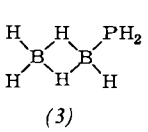
According to the stoichiometry of this reaction, besides μ-phosphinodiborane two other products of molecular formula B_2PH_7 are conceivable, namely bisboranephosphane *(2)* and τ-phosphinodiborane *(3)*.



(1)



(2)



(3)

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However, from the ^{11}B-NMR spectrum of a diethyl ether solution we conclude that only the compound *(1)* is formed (Fig. 1). The four doublets have a spin-spin coupling con-

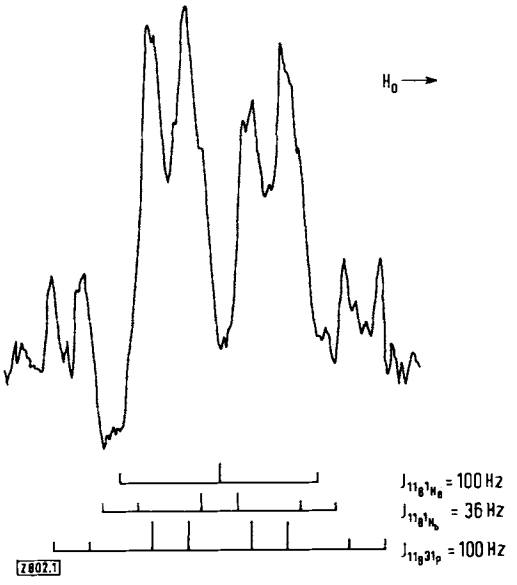

Fig. 1. ^{11}B-NMR spectrum (28.8 MHz) of μ-phosphinodiborane *(1)* in diethyl ether at room temperature [6].

stant of 36 Hz which is typical of systems with B—H—B bridges[3]. The spectrum can be interpreted for μ-phosphinodiborane as a triplet which is further split into doublets by the bridging H and by the P atom. The resulting very similar coupling constants for coupling of ^{11}B with the terminal hydrogen and with phosphorus appear surprising but were found also by *Burg et al.*[2] for various phosphinopentaboranes. τ-Phosphinodiborane *(3)* can also be ruled out as reaction product because it would give a considerably more complicated ^{11}B-NMR spectrum owing to its lower symmetry.

Dilute solutions of *(1)* in diethyl ether are stable below −20 °C. The compound is, however, considerably less stable thermally than μ-aminodiborane[4] and cannot be transcondensed without decomposition or isolated. If the solvent is evaporated off under reduced pressure or if the solution is kept for some time at room temperature, diborane(6) is formed together with a white amorphous residue whose IR spectrum shows the characteristic absorptions of B—H and P—H stretching vibrations at 2400 cm^{-1}. From the amount of diborane that results, decomposition probably involves formation of polymeric phosphinoborane:

$$B_2H_5(PH_2) \rightarrow 1/n(H_2BPH_2)_n + 1/2\,B_2H_6 \quad (2)$$

Experimental:

All the reactions must be carried out in a vacuum or under nitrogen. 90% of the stoichiometric amount of HCl (0.73 mmol) is condensed on $H_2P(BH_3)_2Na$ (68 mg, 0.81 mmol; from H_3BPH_3 and $NaBH_4$[5]) in diethyl ether (20 ml) at −196 °C. Evolution of H_2, which begins at −96 °C, is complete after *ca.* 3 h (0.68 mmol, 93% calculated on HCl used). The precipitate formed is filtered off at −96 °C and characterized as NaCl by its Debye-Scherrer diagram; its IR spectrum contains a weak band at 2400 cm^{-1} which is ascribed to a small proportion of a substance

containing B—H or P—H. B_2H_6 is slowly evolved from the ethereal solution of the boron hydride product *(1)* above 0°C; evolution of B_2H_6 is complete (0.32 mmol, 87%) after 100h at room temperature. Neither PH_3 nor H_2 was found to be formed during this decomposition.

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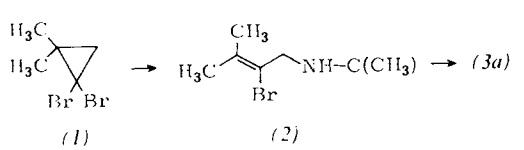
[6] We thank Dr. *M. N. S. Hill,* University of Newcastle-upon-Fyne, for measuring the ^{11}B-NMR spectrum.

Methyleneaziridine-Cyclopropanimine Valence Isomerization[**]

By *Helmut Quast* and *Wolfgang Risler*[*]

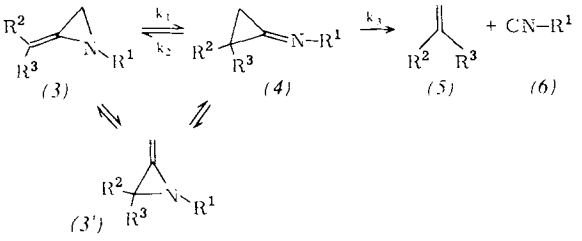
As part of our study of the thermal reorganization of nitrogen analogs of methylenecyclopropane[1,2] we report here the synthesis of a methyleneaziridine substituted at the double bond and also the first proof of the methyleneaziridine-cyclopropanimine valence isomerization that has been repeatedly postulated[3].

Methyleneaziridines unsubstituted on carbon have been known for a long time, but more highly substituted representatives of this class of compounds have not yet been described[4]. By reaction of the bromoallylamine *(2)* [readily accessible by prolonged heating of *(1)* with *tert*-butylamine at 150°C[5]; yield 67—69%, b. p. 89—89.5°C/15 torr] with $NaNH_2$ in liquid NH_3 we obtained 1-*tert*-butyl-2-isopropylideneaziridine *(3a)* (yield 50—60%; b.p. 48°C/14 torr), whose structure follows from elemental analysis and spectroscopic results. IR (CCl_4): 3025 (CH_2), 1792 cm^{-1} (C=C). NMR (CCl_4, 90 MHz): 1.00 (9H/s), 1.70—1.77 ppm (8H/m). MS: 139 (M, 40%), 124 ($M-CH_3$, 11%), 83 ($M-C_4H_8$, 55%), 82 ($M-C_4H_9$, 100%).



(1) *(2)*

(3a) decomposes slowly above 120°C and rapidly at 190°C, *(5a)* and *(6a)* being formed quantitatively. These products can, however, arise only by cheletropic decomposition of the cyclopropanimine intermediate *(4a)*; and this is indicated especially by the fact that the cyclopropanimine *(4b)* also thermolyzes quantitatively in this manner above 140°C[2,6]. If the thermolysis of *(3a)* is followed by NMR spectroscopy, transient signals appear that belong to the isomer *(3'a)* (3.84, 4.06 ppm, >C=CH_2) and, very probably, to the cyclopropanimine *(4a)* (at 1.1 1.3 ppm).



(3) *(4)* *(5)* *(6)* *(3')*

	R^1	R^2	R^3
(a)	$C(CCH_3)_3$	CH_3	CH_3
(b)	$[(CH_3)_2CH]_2CH$	$C(CH_3)_3$	H
(c)	CH_3	H	H
(d)	C_2H_5	H	H
(e)	$C(CH_3)_3$	H	H

Whereas in the case of *(3a)* there is in principle a three-component system [*(3a), (3'a), (4a)*], the kinetics of the thermolysis of the *C*-unsubstituted methyleneaziridines *(3c)*—*(3e)* are expected to be simpler since there the possible transformation *(3)* → *(3')* degenerates to a valence topomerization. We therefore studied the thermolysis of *(3c)*—*(3e)* by NMR spectroscopy[7]. The intensities of the olefinic proton signals of *(3c)*—*(3e)* decreased in a first-order reaction during several half-lives, with $[(3)]=[(3)]_0\exp[-k_1t]$ (Table 1).

Table 1. Rate constants k_1 and activation parameters (for 150°C) of the isomerization *(3)* → *(4)*.

	$10^5 \times k_1$ [s^{-1}]			$\Delta H^{\neq}$	$\Delta S^{\neq}$
	150.0°C	170.0°C	190.0°C	[kcal mol^{-1}]	[cal mol^{-1} deg^{-1}]
(3c)	3.50 ±0.03	21.4 ±0.1	127.5 ±0.8	34.1 ±0.8	1.0 ±1.7
(3d)	1.561 ±0.008				
(3e)	0.085 ±0.002	0.510 ±0.006	3.29 ±0.04	34.8 ±0.2	−4.8 ±0.5

The cyclopropanimines *(4c)*—*(4e)* were always the primary products, undergoing *slow* conversion into ethylene and the isocyanides *(6c)*—*(6e)* (maximal yield 20—25%) and, as thermolysis proceeded, further into unidentified products[8]. For example, from *(3c)* we obtained after 5.5 min at 190°C (half-life 9 min) a mixture containing 71% of *(3c)*, 28% of *(4c)*, 1% of ethylene, and 1% of *(6c)* which remained unchanged at room temperature. The structure of the cyclopropanimine *(4c)* is proved by the AA'BB'X_3 spectrum (AA'BB' part at 1.2 ppm, X_3 part at 3.24 ppm) and decoupling experiments. These results show that the experimentally determined rate constants are to be assigned to the isomerization *(3)* → *(4)* and that here $k_1 \gg k_2$[9], as also for *(4b)*[2,6].

Considering the notorious instability of cyclopropanones[10], it is surprising how stable the corresponding

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imines *(4c)*—*(4e)* are and that they are now readily accessible.

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[5] Following *S. R. Sandler*, J. Org. Chem. *33*, 4537 (1968).

[6] The isomers *(3b)* and *(3'b)* were not detected, so in this case $k_1 > 100\ k_2$ and/or $k_3 \gg k_2$ [2].

[7] 0.16—0.18 mol of benzene per mol of *(3)* served as internal intensity standard.

[8] In the case of *(3e)*, *(5a)* appeared towards the end of the thermolysis and, as consecutive product from *(6e)*, pivalonitrile.

[9] Neither a steady-state approximation nor an equilibrium approximation describes the findings; cf. *C. W. Pyun*, J. Chem. Educ. *48*, 194 (1971).

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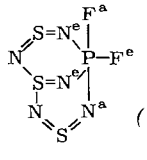
A Bicyclic Phosphorus Trisulfur Pentanitride

By *Herbert W. Roesky* and *Olaf Petersen*[*]

We have isolated a phosphorus-containing sulfur nitride of the composition $S_3N_5PF_2$ (complete elemental analysis) and the unusual structure *(1)* from the products of reaction of phosphorus pentafluoride with *N,N'*-bis(trimethylsilyl)-sulfur diimide[1]. Since the sulfur diimide is in excess at the beginning of the reaction we assume that $F_2P[N{=}S{=}N{-}Si(CH_3)_3]_3$ is first formed and then reacts further with PF_5 to yield *(1)*, $(CH_3)_3SiF$, and $(NPF_2)_n$ in the ratios $1:3:1/n$. It is known that similar reactions of PF_5 do not lead to $(NPF_2)_n$ rings but that derivatives of PF_6^- are formed.



(1)

(1) is a crystalline, golden-yellow solid, extremely sensitive to moisture and sublimable at room temperature in an oil-pump vacuum. The most probable configuration for the pentacoordinated phosphorus is assumed to be a trigonal bipyramid. From ^{31}P- and ^{19}F-NMR studies the fluorine atoms are not exclusively axial (a) and the nitrogen atoms exclusively equatorial (e), as is usual[2]; instead, one finds two doublets in the ^{31}P- and also two doublets in the ^{19}F-NMR spectrum: $\delta_P = +11.5$ ppm; $J(PF^e) = 1008$, $J(PF^a) = 925$, $J(F^aF^e) = 86$ Hz; $\delta_{F^a} = 85.4$, $\delta_{F^e} = 46.8$ ppm (measured at 35 °C; $CFCl_3$ as solvent and internal standard for ^{19}F-NMR, and 85% H_3PO_4 as external standard for ^{31}P-NMR). This accords with the proposed structure *(1)*, in which one fluorine atom is in an axial and another in an equatorial position. The nitrogen atoms assume differing positions for steric reasons. $S_2N_3PF_2$ is found as the ion with the highest mass number ($m/e = 175$, 8%) in the mass spectrum; this fragment arises by loss of NSN from *(1)* and can be regarded as a six-membered ring system; elimination of SN is known to occur in mass-spectrometric investigation of sulfur-nitrogen rings[3]. Other characteristic fragments are: $m/e = 161$ $S_2N_2PF_2$ (48.4%), 129 $NSNPF_2$ (5.1%), 115 $SNPF_2$ (23.7%), 92 S_2N_2 (4%), 78 SNS (9.6%), 69 PF_2 (38.5%), 64 NPF (3.5%), 50 PF (3.7%), 46 SN (100%), 45 NP (1.3%), 32 S (21.8%), 28 N_2 (6.2%). Absorptions (cm^{-1}) were observed in the IR spectrum at 1185 vs, 1138 vs, 1020 w, 1002 m, 960 s, 935 s, 835 s, 728 s, 707 s, and 662 s.

Experimental:

A slow stream of PF_5 is introduced, with stirring, into $[(CH_3)_3SiN]_2S$ (5 g, 0.025 mol) contained at 0 °C in a two-necked flask (250 ml) fitted with a gas inlet tube (not dipping into the liquid) and a final condensation trap (acetone/Dry Ice). When reaction is complete (*ca.* 4 h), unchanged PF_5 can be observed at the exit from the trap, and the flask containing the reaction mixture is then slowly warmed to room temperature. $(CH_3)_3SiF$ collects in the trap, and the product *(1)* (yield 1—5%) sublimes from the dark brown residue at room temperature under oil-pump vacuum.

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A New, Unusually Stable Type of Organo-copper and -silver Compounds

By *Hubert Schmidbaur*, *Jürgen Adlkofer*, and *Wolfgang Buchner*[*]

Replacing simple alkyl groups by trimethylsilylmethyl groups sometimes effects considerable stabilization of organometallic compounds[1,2]. We have now found that this effect of the $(CH_3)_3Si{-}CH_2$ group is greatly exceeded by that of the isoelectronic[3] phosphonium group $(CH_3)_3P^+{-}CH_2$, and that even extremely weak bonds such as the Cu—C and the Ag—C unit[4] become capable of existence under normal conditions when this ligand is used.

Treating anhydrous copper(I) chloride with salt-free trimethylmethylenephosphorane[5] (molar ratio 1:2) in benzene or toluene under an inert gas at room temperature leads, in a homogeneous reaction, to tetramethylphosphonium chloride and a metalated ylide of composition and structure *(1)*.

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$$2\ CuCl + 4\ (CH_3)_3P{=}CH_2 \rightarrow$$

$$2\ [(CH_3)_4P]\ Cl + \ominus[H_3C{-}P^{\oplus}(CH_3){-}CH_2{-}Cu{-}CH_2{-}P^{\oplus}(CH_3){-}CH_3]\ominus$$

(1)

The analogous silver compound *(2)* is better formed from the tetrameric (trimethylphosphane)silver chloride[6] and $(CH_3)_3P{=}CH_2$, and then also in quantitative yield.

$$[(CH_3)_3PAgCl]_4 + 8\ (CH_3)_3P{=}CH_2 \rightarrow$$

$$4\ [(CH_3)_4P]\ Cl + 4\ (CH_3)_3P$$

$$+\ 2\ \ominus[H_3C{-}P^{\oplus}(CH_3){-}CH_2{-}Ag{-}CH_2{-}P^{\oplus}(CH_3){-}CH_3]\ominus$$

(2)

(1) and *(2)* are colorless, crystalline compounds, m.p. 136—138 and 154—155 °C, respectively, soluble in benzene, toluene, CH_2Cl_2, and $CHCl_3$ and sublimable in a vacuum (subl. temp. 100—120 and 150—155 °C/0.1 torr, respectively). They can be recrystallized from toluene/light petroleum (1:1).

The molecular ion M^+ and the fragment ion $(M-15)^+$ appear in the mass spectrum with great intensity and with the isotope distribution characteristic of the metals[7]. The IR spectra (nujol) contain, in addition to the vibrations of the methyl and methylene groups bound to phosphorus, bands at 557 and 509 and at 518 and 470 cm^{-1}, respectively, that can be assigned to $C_2Cu(Ag)$ stretching vibrations. In the ^1H-NMR spectrum[8] of *(1)* two doublets appear with relative areas 3:2, broadened by long-range interactions. P-decoupling simplifies these doublets to two singlets. In the ^1H-decoupled ^{31}P spectrum only one line appears, its position corresponding to that for other phosphonium centers[9] (Table 1). Furthermore, selective decoupling enabled the relative signs of the $J(HCP)$ coupling constants to be determined: $^2J(H_3CP)$ and $^2J(H_2CP)$ are found to have the same sign in the product *(1)*, in contrast to the situation with the free ylide[5,10]. This observation proves rehybridization ($sp^2 \rightarrow sp^3$) of the ylide carbanion upon coordination to the metal[10,11].

Table 1. ^1H- and ^{31}P-NMR spectra of *(1)* and *(2)* (in C_6D_6 and $C_6D_5CD_3$; TMS and H_3PO_4, respectively, as external standards, 35 °C).

	(1)	*(2)*
^1H, δCH_3 [ppm]	− 0.5, d	− 0.5,d
δCH_2	+ 0.08, d	0.0, dd
^{31}P, δP [ppm]	−24.2, s [a]	−28.6, t [a]
$^2J(H_3CP)$	−11.6 Hz	−11.6 Hz
$^2J(H_2CP)$	−13.4 Hz	−12.0 Hz
$^4J(H_3CPCH_2)$	+ (small)	+ (small)
$^2J(AgCP)$	—	± 9.7 Hz [b]
$^2J(AgCH)$	—	± 9.8 Hz [b]

[a] ^1H decoupled.
[b] $J(AgCP)$ and $J(AgCH)$ have the same sign. The relation to the other coupling constants is not yet known.

The NMR spectra of *(2)* correspond to those of *(1)* but an additional effect provides new structural proof: the CH_2 resonances appear here as a doublet of doublets (1:1:1:1), on P-decoupling as a doublet, and the ^{31}P resonance appears as a 1:2:1 triplet. These multiplicities result from the $^1H{-}C{-}^{109,107}Ag$ and $^{31}P{-}C{-}^{109,107}Ag$ interactions, which to our knowledge have not been observed previously[12].

For both ring systems we assume linear C—Cu(Ag)—C units and tetrahedral PC_4 units as components of an eight-membered ring.

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[7] We thank Dipl.-Chem. *N. Pelz* for these measurements (70 eV, inlet temp. 30 °C).

[8] We thank *C. P. Kneis* for measuring numerous spectra.

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Phosphorus Ylides as Structural Units in Organogold Compounds[**]

By *Hubert Schmidbaur* and *Rainer Franke*[*]

Organometallic gold(I) compounds are generally not very stable and can be isolated only if they contain stabilizing ligands[1]. In a study of the ligand function of ylides we have now shown that not only the first but also a second Au—C σ-bond is stabilized to an unexpectedly great extent by a neighboring onium center. In this way it has been possible to synthesize compounds containing a structural unit $R{-}Au{-}R^{\ominus}$, which is isoelectronic with the R—Hg—R group.

Treating (trimethylphosphane)gold chloride with trimethylmethylenephosphorane[2] in benzene or toluene affords, depending upon the molar proportions of the reactants, the gold-phosphonium salts *(1)* and *(2)* in quantitative yield. In the second stage of the reaction the phosphane ligand is removed from the gold atom.

(1), m.p. 178—181 °C, is readily soluble in CH_2Cl_2 and in that solvent at −60 °C shows the expected ^1H- and ^{31}P-NMR spectra. Structural evidence is provided especially by the coupling constants $J(^{31}P{-}Au{-}C{-}^1H) = +9$ Hz and $J(^{31}P{-}C{-}^1H_2) = -14.5$ Hz. The signs of the PCH_2 interaction[3] prove the rehybridization $sp^2 \rightarrow sp^3$ of the ylidic C atom on coordination. With *(2)*, m.p. 170 °C (dec), the ^1H spectrum shows the CH_2

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doublet with evident broadening due to long-range $^4J(^{31}PCAuC^1H)$ and $^4J(^1HCAuC^1H)$ coupling. The IR spectra contain characteristic bands of Au—C stretching vibrations at 561/550 *(1)* or 549 cm^{-1} *(2)*.

$$(CH_3)_3P{\rightarrow}Au{-}Cl + (CH_3)_3P{=}CH_2$$

$$\downarrow$$

$$[(CH_3)_3P{\rightarrow}Au{-}CH_2{-}\overset{\oplus}{P}(CH_3)_3]\ Cl^{\ominus} \quad (1)$$

$$+(CH_3)_3P{=}CH_2 \;\Big|\; -(CH_3)_3P$$

$$\downarrow$$

$$[(CH_3)_3\overset{\oplus}{P}{-}CH_2{-}\overset{\ominus}{Au}{-}CH_2{-}\overset{\oplus}{P}(CH_3)_3]\ Cl^{\ominus}$$

$$(2)$$

Even the more weakly basic ylides mono- and bis-(trimethylsilyl)methylenetrimethylphosphorane[4] form one and two Au—C bonds, respectively, and yield the aurated onium salts *(3)*, *(4)*, and *(5)*.

$$(CH_3)_3P{\rightarrow}Au{-}\underset{\oplus}{C}H(Si(CH_3)_3){-}P(CH_3)_3\ Cl^{\ominus}$$

$$(3)$$

$$(CH_3)_3Si{-}\underset{\oplus}{C}H{-}\overset{\ominus}{Au}{-}\underset{\oplus}{C}H{-}Si(CH_3)_3\ (P(CH_3)_3,\ P(CH_3)_3)\ Cl^{\ominus}$$

$$(4)$$

$$(CH_3)_3P{\rightarrow}Au{-}\underset{\oplus}{C}(Si(CH_3)_3)_2{-}P(CH_3)_3\ Cl^{\ominus}$$

$$(5)$$

Introducing the large organosilicon ligands increases the solubility of the substances in weakly polar solvents, so that high concentrations can be achieved. The decomposition temperatures for *(3)* to *(5)* are at or above 150 °C.

The ^{31}P-NMR spectrum of *(5)* contains an AB system with $\delta P^{III} = -2.82$, $\delta P^{V} = -23.4$, and $^3J(^{31}PAuC^{31}P) = 17$ Hz[5].

When an excess of the ylide reacts with $(CH_3)_3PAuCl$, or with *(1)* or *(2)*, dehydrohalogenation and precipitation of $[(CH_3)_4P]Cl$ occur, with formation of the novel eight-membered heterocycle *(6)*, m. p. 216—218 °C.

Like its copper and silver analogs[6], this dimeric gold(I)-dimethylphosphonium bismethylide is soluble in organic solvents such as CH_2Cl_2 and $CHCl_3$ and is volatile in a vacuum. In the mass spectrum[7] the molecular ion

$$H_3C{-}\overset{\oplus}{P}(CH_2{-}\overset{\ominus}{Au}{-}CH_2{-}CH_3)(CH_2{-}Au{-}CH_2{-}CH_3)\overset{\oplus}{P}{-}CH_3 \quad (6)$$

appears with great intensity at $m/e = 572$; νAuC occurs as a strong IR band at 551 cm^{-1}. *(6)* is remarkably insensitive to air and moisture. ^{1}H-NMR: $\delta CH_3P = -1.65$ ppm (d, 3 H), $J(HCP) = -11.9$ Hz; $\delta CH_2P = -0.93$ ppm (d, 2 H), $J(H_2CP) = -12.3$ Hz. ^{31}P-NMR: $\delta P = -32.2$ ppm (s, ^{1}H decoupled)[8].

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Column-Chromatographic Separation of Neutral Sugars on a Dihydroxyboryl-Substituted Polymer[*]

By *Konrad Reske* and *Herbert Schott*[*]

The separation of ribo- and deoxyribo-nucleic acid units on dihydroxyboryl-substituted polymers ("boric acid gels") was reported recently[1]. Meanwhile we have been able to separate mixtures of mono- and oligo-saccharides by means of this gel (Figs. 1 and 2).

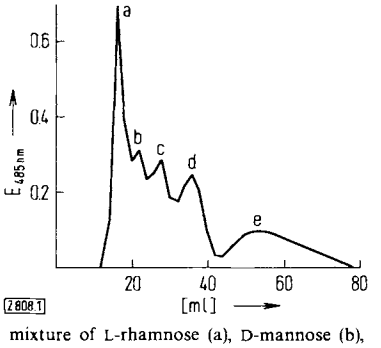

Fig. 1. Elution profile of a mixture of L-rhamnose (a), D-mannose (b), D-galactose (c), D-glucose (d), and D-ribose (e) on "boric acid gel"; for conditions see Experimental.

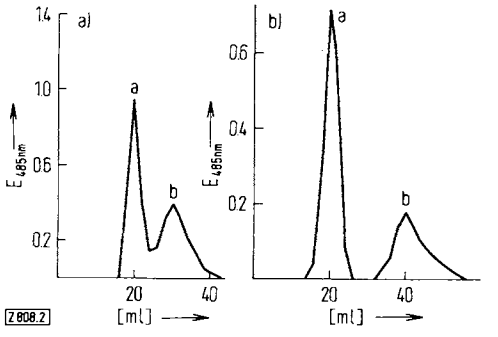

Fig. 2. a) Separation of maltose (a) and isomaltose (b) and b) of lactose (a) and raffinose (b) on "boric acid gel"; for conditions see Experimental.

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[3] *H. Schmidbaur*, *W. Buchner*, and *D. Scheutzow*, Chem. Ber. *106*, 1251 (1973); *H. Schmidbaur* and *W. Tronich*, *ibid. 101*, 3556 (1968); see also *K. Hildenbrand* and *H. Dreeskamp*, Z. Naturforsch., in press (personal communication). — We thank Dr. *W. Buchner* and *C. P. Kneis* for the NMR measurements.

[4] *H. Schmidbaur* and *W. Tronich*, Chem. Ber. *100*, 1032 (1967); *N. E. Miller*, Inorg. Chem. *4*, 1458 (1965); J. Amer. Chem. Soc. *87*, 390 (1965).

[5] ^{1}H-decoupled, H_3PO_4 ext., in CH_2Cl_2 at 30 °C. — ^{1}H-NMR (TMS ext.): $\delta CH_3P = -1.77$ and -2.09 ppm (d, 9 H), $J(HCP) = 10.5$ and 12.5 Hz, respectively; $\delta CH_3Si = -0.42$ ppm (s, 18 H).

[6] *H. Schmidbaur*, *J. Adlkofer*, and *W. Buchner*, Angew. Chem. *85*, 448 (1973); Angew. Chem. internat. Edit. *12*, 415 (1973).

[7] Satisfactory analyses are available for all the compounds named here. We thank Dipl.-Chem. *H. Pelz* for the mass spectra.

[8] These signals are further split by long-range interactions.

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We have found the complexes of the sugar with the gel matrix to correspond to the sugar-borate complexes in solution; their formation is pH-dependent. Optimal separation is obtained at pH > 9. The configuration of the sugar hemiacetal ring is of special importance for complex formation as it is well known that sugars form borate complexes preferentially in their furanose form[2]; Fig. 1 confirms this finding. Furanose formation of the terminal glucose also provides an explanation for the separation of maltose from isomaltose (Fig. 2a). An increase in the number of *cis*-hydroxyl groups leads to more extensive complex formation; thus lactose and raffinose can be separated quantitatively (Fig. 2b). The disaccharide pairs maltose and cellobiose, and maltose and lactose, however, show only very slight differences in their elution maxima since none of them yields a furanose form and they all contain the same number of *cis*-hydroxyl groups.

Compared with the procedures used hitherto[3-5], chromatography on "boric acid gels" offers the following advantages:

1. The use of volatile buffers permits rapid working up of the fractions since the separated sugar components can be isolated quantitatively in high purity without desalting. Also the absence of borate residues is of particular importance in structural chemical work with oligosaccharides[6].

2. By suitable choice of gel and gel volumes both mono- and oligo-saccharides can be optimally separated, even if they differ only very slightly in complex formation constants.

Experimental:

A chromatographic column (1/20 cm) is filled with swollen "boric acid gel"[1], then washed with 0.5 N HCl, and finally washed neutral. The sugar mixture (each 1 mg per mono- or oligo-saccharide) is dissolved in the eluant (0.2 ml), placed on the column and eluted with 0.1% aqueous ammonia (pH = 10.5), fractions of 4 ml per hour being collected. Aliquot parts (0.2 ml) of the fractions are monitored by the phenol/sulfuric acid reagent for presence of sugars[7] (test batch: 0.2 ml of fraction solution + 0.1 ml of 90% phenol + 1 ml of H_2O, shake, then add 3 ml of concentrated H_2SO_4). The sugars that are separated are identified by borate electrophoresis.

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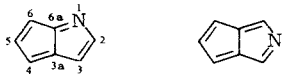
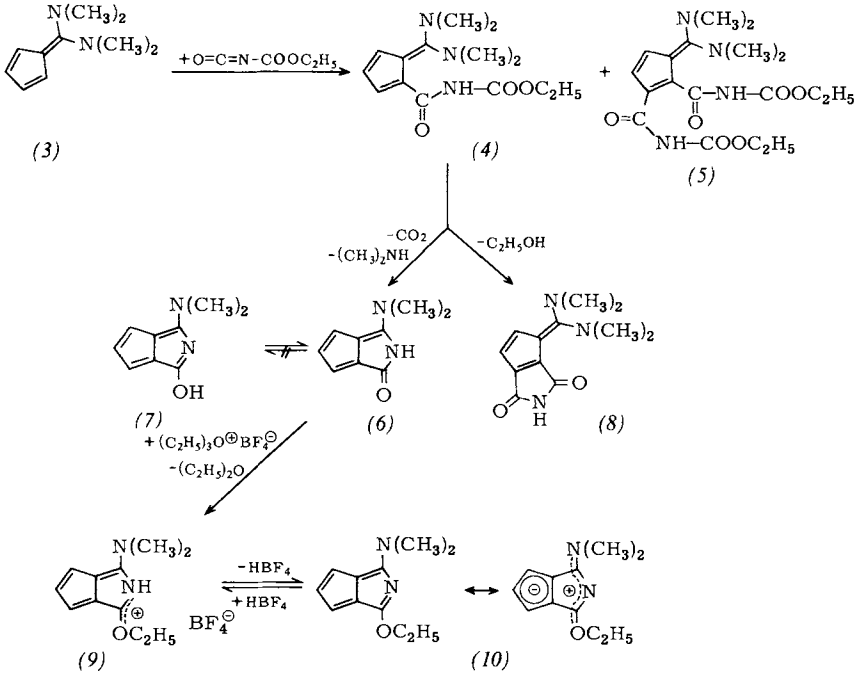
A Stable 2-Azapentalene[**]

By *Klaus Hafner* and *Frank Schmidt*[*]

After the synthesis of simple carbocyclic pentalenes[1] the aza analogs attract particular interest because their properties are likely to depend markedly on the position of the nitrogen atoms. As 8π-electron systems 1- *(1)* and 2-azapentalene *(2)*, as well as polyazapentalenes with C-fusion of the two five-membered rings, should not be "aromatic". In spite of many attempts no such bicyclic azapentalene has hitherto been prepared. The thermal instability of benzo[*b*]- and benzo[*f*][1]azapentalene precludes their



(1) *(2)*



(3) *(4)* *(5)* *(6)* *(7)* *(8)* *(9)* *(10)*

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isolation[2]. Neither the various known azapentalene anions[3] nor the "aromatic" 1,3a,4,6a-tetraazapentalenes[4] and 3a,6a-diazapentalenes[5] allow valid conclusions about the properties of *(1)* and *(2)*. Both the structures *(1)* and *(2)* formally combine a pentafulvene and an azapentafulvene system, and this consideration led us, starting from 6,6-bis(dimethylamino)fulvene *(3)*[6], to synthesize the first stable 2-azapentalene.

(3) reacts with ethyl isocyanatoformate in acetonitrile at 20 °C, yielding 6,6-bis(dimethylamino)-1-[*N*-(ethoxycarbonyl)carbamoyl]fulvene *(4)*[7] [yield 22%; yellowish crystals, m. p. 150—151 °C; UV (dioxane): λ_{max} (log ε) = 258 (4.25), 335 (3.93), 369 nm (4.13); 60-MHz-NMR ($CDCl_3$): τ = 2.14 (broad, NH); double doublet centered at 3.37 (J = 3.5 Hz and J = 2.0 Hz) and 3.77 (J = 3.5 Hz and J = 2.0 Hz, 2-H, 4-H), 3.96 (t, J = 3.5 Hz, 3-H), 5.79 (q, CH_2), 6.96 (s, $2N(CH_3)_2$), 8.71 (t, CH_3)], and 7% of 6,6-bis(dimethylamino)-1,2-bis-(*N*-ethoxycarbonyl)carbamoyl]fulvene *(5)* (pale yellow crystals of m. p. 172—174 °C).

In boiling pyridine/H_2O (80 h), *(4)* undergoes intramolecular cyclization with loss of CO_2 and $(CH_3)_2NH$, yielding 3-(dimethylamino)-2*H*-2-azapentalen-1-one *(6)* [yield 47%; orange needles, dec. > 250 °C; UV (CH_3OH): λ_{max} (log ε) = 217.5 (4.39), 252 (4.14), 360 (4.02), 444 nm (3.44); IR (Nujol): 3180 (NH), 1685 cm^{-1} (CO); 60-MHz-NMR ([D_6]DMSO): τ = 0.42 (broad, NH); A_2B system: τ_A = 3.75 (4-H, 6-H), τ_B = 3.96 (5-H) (J_{AB} = 3.4 Hz), 6.71 (s, N—CH_3), 6.78 (s, N—CH_3)]. In addition, 0.5% of 6,6-bis(dimethylamino)fulvene-1,2-dicarboximide *(8)* was isolated (yellow crystals, m. p. 174—175 °C). The IR and UV spectra of the lactam *(6)* give no evidence for an equilibrium with the pentalenoid lactim *(7)*.

As expected, *(6)* can be converted by triethyloxonium tetrafluoroborate in CH_2Cl_2 at 0 °C by *O*-alkylation into the tetrafluoroborate *(9)*. The deprotonation of *(9)* by 50% aqueous K_2CO_3 solution leads to the lactim ether, 3-(dimethylamino)-1-ethoxy-2-azapentalene *(10)*, isolated as bluish-violet needles of m. p. 78—79 °C (yield 37%). The 100-MHz-NMR spectrum (in $CDCl_3$) of *(10)*, which proves its structure, resembles that of 1,3-bis(dimethylamino)pentalene[8] regarding the chemical shifts of the five-membered ring protons and provides no evidence for an induced ring current. [ABX system at $\tau_{A,B} \approx 3.85$ (4-H, 6-H) and τ_X = 4.15 (5-H), 6.66 (s, N—CH_3), 6.76 (s, N—CH_3), 5.57 (q, OC_2H_5), 8.57 (t, OC_2H_5).] The UV spectrum of *(10)* (in *n*-hexane) agrees reasonably with the values obtained by an SCF—CI calculation[9] and shows absorption maxima at 221 (log ε = 4.36), 274 (4.03), 281 (sh), 393 (4.16), and 598 nm (2.75). The spectrum resembles that of 1,3-bis(dimethylamino)pentalene. However, as with azulenes[10], replacing a methine group of a pentalene by nitrogen at a position of high charge density causes a hypsochromic shift of the longest-wavelength maximum.

In atmospheric oxygen *(10)* is stable for some days at room temperature, and shows a marked basicity (dissolves in 0.1 N acetic acid). It is converted by proton acids, in a quantitatively reversible reaction, into the conjugate acid *(9)* [perchlorate, carmine-red needles, dec. > 195 °C; UV (CH_2Cl_2): λ_{max} (log ε) = 260 (4.00), 267 (4.01), 272 (3.87), 372 (4.08), 381 (4.11), 522 nm (3.24); 100-MHz-NMR (CD_3CN): τ = 0.91 (broad NH), ABX system with $\tau_{A,B} \approx 3.15$ (4-H, 6-H) and τ_X = 3.60 (5-H), 6.63 (s, N—CH_3), 6.70 (s, N—CH_3), 5.40 (q, OC_2H_5), 8.48 (t, OC_2H_5)].

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German version: Angew. Chem. 85, 450 (1973)

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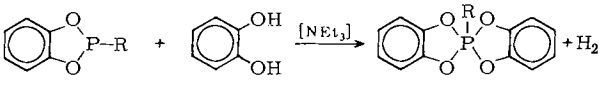
Alkyl- and Aryl-hydridobis(*o*-phenylenedioxo)-phosphate(1−), a Stable Spiroanion Containing Hexacoordinated Phosphorus[**]

By *Markus Wieber* and *Keywan Foroughi*[*]

Reactions of derivatives of quinquevalent phosphorus often occur by way of an intermediate containing a hexacoordinated phosphorus atom[1]. When converting trivalent into quinquevalent phosphorus by the reaction[2]

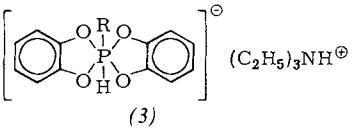


(1) *(2)*

R = CH_3, C_6H_5

we have isolated the first stable intermediate containing hexacoordinated phosphorus.

Hydridomethyl (or phenyl)bis(*o*-phenylenedioxo)phosphate(1−) can be obtained as its triethylammonium salt *(3)* by treating 1,3,2-benzodioxaphospholes *(1)* with pyrocatechol and triethylamine in the molar ratio 1 : 1 : 1.



(3)

R = CH_3, C_6H_5

As shown by the NMR spectra (Table 1), the products exist, even in polar solvents, in the spiro form with coor-

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dination number 6 for the phosphorus atom and a P—H bond[3] and not in the conceivable open form (discussed previously[4, 5]) with coordination number 5 and an O—H bond.

Pure *(3)* decompose exothermally[6] at 83 °C ($R=CH_3$) or 128 °C ($R=C_6H_5$) with dehydrogenation, *i.e.* with liberation of stoichiometric amounts of triethylamine and hydrogen and formation of the spirophosphorane *(2)*.

(3) → *(2)* + H_2 + $(C_2H_5)_3N$

This decomposition explains why triethylamine acts as catalyst in the first of our reaction schemes.

Table 1. NMR data for the anions of *(3)* dissolved in CD_3CN.

^{1}H-NMR (100 MHz, TMS external, δ in ppm, *J* in Hz)			
$R=CH_3$:	δ = 0.6	3 H/d	$J_{P\text{-}C\text{-}H_3}=10.7$
		/d	$J_{H\text{-}P\text{-}C\text{-}H_3}=1.5$
	= 6.4	1 H/d	$J_{P\text{-}H}=620$
		/q	$J_{H_3\text{-}C\text{-}P\text{-}H}=1.5$
	= 6.0	8 H/m	
$R=C_6H_5$:	δ = 6.7	1 H/d	$J_{P\text{-}H}=642$
	= 6.9	5 H/m	
	= 6.0	8 H/m	
^{31}P-NMR (40.5 MHz, H_3PO_4 external, δ in ppm)			
$R=CH_3$:	δ = +113.5		
$R=C_6H_5$:	δ = +108.8		

Experimental:

An ethereal solution of pyrocatechol is slowly added dropwise, with ice-cooling and stirring, to a solution of equivalent amounts of the phosphole and triethylamine under N_2. The white precipitate formed is filtered off on a frit, washed with ether, and dried in a vacuum. The yield of the very hygroscopic compound *(3)* is >95%.

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[6] Thermal Analyzer Mod. 990, Du Pont.

Anion Structure of Tributylammonium Decatungstate $[HN(C_4H_9)_3]_4W_{10}O_{32}$

By *Joachim Fuchs, Hans Hartl*, and *Wolfgang Schiller*[*]

When a tungstate solution is acidified, the oxide hydrate $WO_3 \cdot 2H_2O$ is formed. The aggregation process leads through numerous intermediates (polyanions), some of which can be demonstrated by physicochemical methods. In weakly acid solutions the hexameric paratungstate A[1], $W_6O_{20}(OH)^{5-}$ or $W_6O_{19}(OH)_3^{5-}$, dominates, but in more strongly acid solution the decatungstate ion $W_{10}O_{32}^{4-}$[2] The structures of these acidification products have so far been unknown; the only structures clarified are those of the polytungstates formed during more protracted aging processes (paratungstate Z[3], metatungstate[4], *etc.*).

The tributylammonium salt $[HN(C_4H_9)_3]_4W_{10}O_{32}$[2] was the first crystalline decatungstate to be obtained. It is formed by precipitation from a freshly acidified tungstate solution ($1.6\,H^+/WO_4^{2-}$) with tributylammonium acetate or by treating $WO_3 \cdot H_2O$ with a solution of tributylamine in acetone or by hydrolysis of tetraethyl tungstate(VI), $WO(OC_2H_5)_4$, in the presence of tributylamine. It can be recrystallized from methanol.

The structure of $[HN(C_4H_9)_3]_4W_{10}O_{32}$ has now been elucidated by three-dimensional diffractometer data with evaluation of 4973 independent reflections ($R=7.7\%$). The unit cell, of space group $P2_1/c$ with $a=12.159\pm0.006$, $b=13.185\pm0.006$, $c=24.849\pm0.013$ Å, and $\beta=95.36\pm0.10°$, contains two formula units. Figure 1 shows the idealized structure of the polyanion with the symmetry 4/mmm (D_{4h}).

Two W_5O_{18} units are bonded mirror-symmetrically through four common oxygen atoms with formation of an octahedral space. The polyanion contains four differing groups of oxygen atoms: 10 terminal O atoms (O_t), 16 O atoms (O_k) each bridging two W atoms to each other through edges of octahedra, 4 O atoms (O_e) bridging two W atoms through corners of octahedra, and 2 O atoms (O_c) each coordinated to five W atoms. The W—O distances within the polyanion are: W—O_t = 1.68—1.76 Å; W—O_k = 1.86—2.01 Å; W—O_e = 1.88—1.94 Å; and W—O_c = 2.28—2.34 Å.

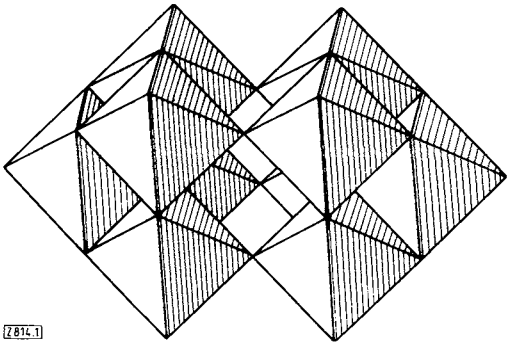

Fig. 1. Structure of the decatungstate ion $W_{10}O_{32}^{4-}$.

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German version: Angew. Chem. *85*, 417 (1973)

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Polysulfide Radical Ions[**]

By *Fritz Seel* and *Hans-Joachim Güttler*[*]

At the present time much interest is being shown in the singly charged polysulfide(−1) radical ions, S_2^- (yellowish-

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green), S_3^- (blue), S_4^- (red), as colored particles in solutions of polysulfides(−2) in superheated water, electron pair donor ("EPD") solvents such as dimethylformamide (DMF), dimethyl sulfoxide, and hexamethylphosphorotriamide, melts of potassium thiocyanate and borate glasses, as well as of doped alkali-metal halides and as colored species of ultramarine[1]. Most authors, however, failed to assign the color and charge of the particles correctly. We have now found that one can solve this problem convincingly by quantitative spectrophotometric titration of 1 to 4×10^{-3} molar solutions of *disodium tetrasulfide* in DMF[2] with milligram portions of sulfur under *absolute* exclusion of oxygen.

100 ml of polysulfide solution was placed in a "two-bulb" apparatus with a connection to a vacuum line; to this apparatus was fused a quartz cuvette 1 mm thick (d) and a glass tube with a magnetic closure. The glass tube also held 20 small glass beakers each containing 1 mg of sulfur (see Fig. 1).

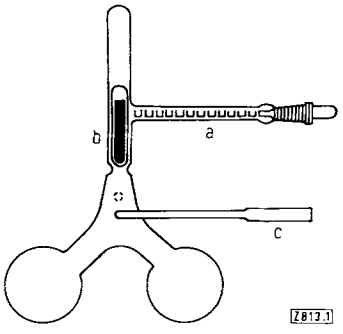

Fig. 1. Apparatus for titration of solutions with solid substance with exclusion of air. a, small beakers; b, magnetic closure; c, cuvette.

The extinction curves in the range 12000 to 30000 cm^{-1} show successive development of three absorption maxima, at 25300, 16200, and 19500 cm^{-1}, with two isosbestic points, at 23300 and 18100 cm^{-1}, which impressively demonstrate the changes $S_2^-\rightarrow S_3^-\rightarrow S_4^-$. A disproportionation equilibrium $4S_2^-\rightleftarrows 2S_3^- + S_2^{2-}$ explains why the *bluish-green* solutions of pure sodium tetrasulfide already display the band at 16200 cm^{-1}. Solutions with S : Na = 1.9 contain only *green* S_2^- alongside polysulfide(−2). *Blue* S_3^- is formed almost quantitatively when S : Na = 3. (Cf. Fig. 2.) Here the value of the quotient $E_{16200}/d\cdot c_{Na}$ ($\approx$4800) is almost independent of the concentration c_{Na} of sodium ions when $c_{Na}<10^{-3}$ g-atom/l. This means that in very dilute solution S_3^- is only slightly associated to S_6^{2-}. The association S_n^- to S_{2n}^{2-} is also indicated by the finding that the two isosbestic points are no longer so well developed in more concentrated solutions.

An argument for the correctness of the assignment is that the band due to S_3^- at 16200 cm^{-1} in a solution as well as the band due to S_3 at 24400 cm^{-1} in a matrix[3] show a vibrational structure. That, on addition of still more sulfur, S_3^- is actually replaced by *red* S_4^- is shown by the tangent placed in Figure 2 near the maximum of the curve for E_{16200} and leading to the point S/Na = 4 on the abscissa. However, addition of sulfur in excess of S/Na = 4 does not lead to even approximately quantitative formation of S_4^- ($E_{19500}/d\cdot c_{Na}\approx 2200$). Clearly an equilibrium sets in between S_4^- and S_3^- plus free sulfur. At very high sulfur concentrations the proportion of S_3^- decreases faster than that of S_4^- increases. It must be assumed that under these conditions polysulfide(−2) ions, S_n^{2-} ($n>8$), are formed and that these do not dissociate to radical ions $S_{>4}^-$. The explanation of this is that normal polysulfide(−2) ions form a structurally homologous series of chain molecular ions and not the radical ions S_2^-, S_3^-, S_4^-, as already shown by the various colors. Evidently

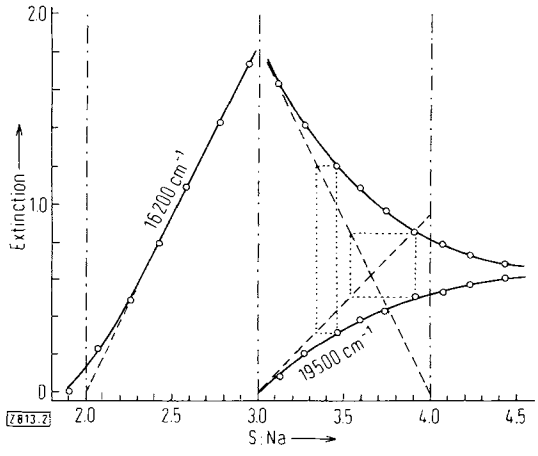

Fig. 2. Change in the maximal extinction of S_3^- and S_4^- in the visible region on titration of a 2.05×10^{-3} M solution of disodium tetrasulfide in dimethylformamide at 25 °C (layer thickness 1 mm).

only those radical fragments are formed that are stabilized by electron delocalization effects. (The ESR signal of S_4^- indicates that the four sulfur atoms form a ring[4].)

As expected, the equilibrium $nS_4^-\rightleftarrows nS_3^- + S_n$ is concentration-dependent. That it is also temperature-dependent is shown by the fact that violet solutions, which contain both S_3^- and S_4^-, become pure blue when warmed to 100 °C and red when cooled to 0 °C. Cooling to near the melting point of dimethylformamide (−61.0 °C) leads to *yellow* polysulfide(−2) solutions which are characterized by a first extinction maximum at 21000 cm^{-1}. The square of the quotient of the extinction values of S_4^- and S_3^- is proportional to the concentration of excess sulfur to a very good approximation in the range Na : S = 3 to 3.5; this is an indication that in EPD solvents the cleavage of S_8-sulfur to S_2 molecules is catalyzed by nucleophilic attack of sulfide.

In agreement with other authors[4,5] we have found no hyperfine splitting in the ESR signals of anionic sulfur radicals due to formation of long-lived ionic associates with Na^+ (*g* factor of S_3^-: 2.0280). That the signal width is very large particularly in dilute solutions (110—120 G) indicates a rapid exchange of electrons within larger, short-lived ionic associates with at least two S_n^- ions:

$$S_n^-\,Na^+\,S_n^- \rightleftharpoons S_nNa \qquad S_n^- \rightleftharpoons S_nNa^+S_n^{2-}$$

or rapid equilibration between polysulfide(−1) ions on the one hand and polysulfide(−2) ions and small sulfur molecules on the other.

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π-Ionization Potentials of Alkylfulvenes, or the Limitations of Koopmans' Theorem[**]

By *Franz Brogli, Patricia A. Clark, Edgar Heilbronner,* and *Markus Neuenschwander*[*]

The so-called Koopmans' theorem states that vertical ionization potentials $I_{v,j}$, taken as negative, can be equated to the Hartree-Fock-SCF orbital energies ε_j:

$$\varepsilon_j = -I_{v,j} \tag{1}$$

where ε_j denotes the SCF orbital energy of that orbital ψ_j in the neutral singlet molecule M which loses the electron e^- in the (photo)ionization process

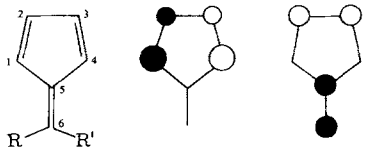
$$M \xrightarrow{h\nu} M^+(\psi_j) + e^- \tag{2}$$

That theorem (1) must fail in many cases was discussed in detail already by *Koopmans* in his fundamental paper[1] (cf. [2]). Photoelectron spectroscopy has recently provided numerous examples showing that, in particular, reorganization of the electrons remaining in the radical cation $M^+(\psi_j)$ results in considerable corrections. An extreme example is provided by bis(π-allyl)nickel, whose first ionization potential $I_v = 7.85$ eV[3] corresponds to the removal of an electron from the $9a_g$ orbital of the neutral molecule. This is an almost pure Ni-3d orbital[4], which, however, is not the highest occupied molecular orbital, but the 13th orbital (!), counted from the highest occupied orbital $7a_u$. *Ab initio* calculations by *Rohmer* and *Veillard*[5] showed that $\varepsilon(9a_g) = -18.3$ eV, whereas they obtained only $\Delta E(M^+(9a_g)) = -7.9$ eV for the energy of $M^+(9a_g)$ after relaxation of the electrons, this value being in good agreement with experiment.

In spite of the well known and well understood shortcomings of eq. (1) it is nevertheless often implicitly assumed that Koopmans' theorem is valid at least in the weakened form

$$\delta\varepsilon_j = -\delta I_{v,j} \tag{3}$$

i.e. that, for example, changes $\delta I_{v,j}$ in the ionization of a parent compound M due to substitution can be predicted from orbital energy shifts $\delta\varepsilon_j$ calculated by perturbation theory (cf. *e.g.* [6]). The following example of alkyl-substituted fulvenes *(1)* (R,R') will show that even this is true only under quite definite conditions.



(1) (R, R') $1a_2$ $2b_1$ (4)

The PE spectrum of fulvene *(1)* (H,H) shows two bands, at $I_{v,1} = 8.55$ and $I_{v,2} = 9.54$, which according to eq. (2) are to be correlated with the π-orbitals $1a_2$ and $2b_1$[7]. The π-orbital diagrams shown in (4) for $1a_2$ and $2b_1$ are those obtained from an HMO model.

Since $1a_2$ possesses a nodal plane through centers 5 and 6, the influence of the substituents R,R' would not be expected to cause any shift $\delta I_{v,1}$, whereas $\delta I_{v,2}$, because of the finite value of the π-orbital $2b_1$ at positions 5 and 6, should differ distinctly from zero and should be negative. This expectation is supported from a theoretical standpoint by calculations employing EHT[8], MINDO/2[9], SPINDO[10], and INDO[11] procedures[12] and assuming eq. (1) or (3) to be valid. In sharp contrast, however, the experiment (see Table 1) shows that $\delta I_{v,1}$ is of the same order of magnitude as $\delta I_{v,2}$.

Table 1. π-Ionization potentials of alkyl-substituted fulvenes *(1)* (R,R') in eV.

(1) (R,R') R	R'	$I_{v,1}$	$I_{v,2}$	$-\delta I_{v,1}$	$-\delta I_{v,2}$
H	H	8.55	9.54	0.00	0.00
H	Me	8.31	9.09	0.24	0.45
H	Et	8.27	9.03	0.28	0.51
H	*n*-Pr	8.23	8.95	0.32	0.59
H	*i*-Pr	8.25	8.97	0.30	0.57
H	*n*-Bu	8.24	8.96	0.31	0.58
H	*i*-Bu	8.17	8.91	0.38	0.63
H	*t*-Bu	8.11	8.88	0.44	0.66
Me	Me	8.08	8.75	0.47	0.79
Et	Et	7.99	8.63	0.56	0.91
n-Pr	*n*-Pr	7.92	8.53	0.63	1.01
$-CH_2(CH_2)_2CH_2-$		7.93	8.57	0.62	0.97

From the values in Table 1 one calculates that (in eV)

$$\delta I_{v,2} = (-0.0694 \pm 0.0297) + (1.503 \pm 0.071)\,\delta I_{v,1} \tag{5}$$

The correlation coefficient $r = 0.989$ shows that $\delta I_{v,1}$ and $\delta I_{v,2}$ are strictly linearly dependent on one another. The standard deviation from the regression line (5) amounts to only 0.042 eV. Since the regression line (5) does not significantly by-pass the origin on a 95% confidence level we can write for all the derivatives *(1)* (R,R'):

$$\delta I_{v,2}/\delta I_{v,1} = 1.5 \tag{6}$$

The reason why $\delta I_{v,1} \neq 0$ is at once evident if one carries out an SCF calculation for the radical cation produced from *(1)* (H,H) according to process (2) in one or the other of the two states $^2A_2$ (ground state; single occupation of $1a_2$) and $^2B_1$ (first excited state; single occupation of $2b_1$). The results collected in Table 2 have been obtained by the INDO procedure[11,12]. It can be seen that for the ground state $^2A_2$ the "Koopmans process" gives rise to changes $\Delta Q(1a_1)$ in the positive charge at positions 1, 2, 3, and 4 [cf. the orbital diagram (4)] and to zero change at positions 5 and 6. Relaxation of the electrons in the radical cation leads to the positive "holes" being filled by a drift of π- and σ-electrons. As a consequence removal of electrons from the exocyclic double bond causes a positive charge of $Q_6^+(1a_2) = 0.234$ unit charge at position 6. Taking the electron relaxation into consideration one finds, on comparing $Q_6^+(2b_1)$ with $Q_6^+(1a_2)$, that

$$Q_6^+(2b_1)/Q_6^+(1a_2) = 1.61 \tag{7}$$

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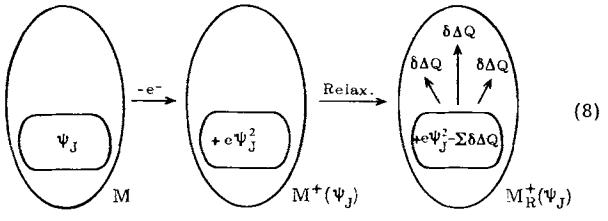
i.e., a value that agrees closely with the ratio of the observed shifts given in (6).

Table 2. Theoretical calculation of the electron relaxation in fulvene radical cations. All charges and changes of charge are given in $e/1000$ (e = unit charge) to the nearest whole number. Method of calculation: INDO [11]. Q = charge in the neutral fulvene *(1)* (H,H). $Q^+(1a_2)$, $Q^+(2b_1)$ = charge in the fulvene radical cation after relaxation has been taken into account. $\Delta Q(1a_2)$, $\Delta Q(2b_1)$ = change in charge due to removal of one electron from the orbitals $1a_2$ and $2b_1$, respectively ("Koopmans ionization process"). $\delta\Delta Q$ = change in charge due to relaxation of the π- or σ-electrons. Note: $Q^+(\psi) = Q(\psi) + \Delta Q(\psi) + \delta\Delta Q_\pi + \delta\Delta Q_\sigma$, within rounding off error.

		Ground state $^2A_2$				1st Excited state $^2B_1$			
		Ionization from $1a_2$; 1st band				Ionization from $2b_1$; 2nd band			
Position	Q	$\Delta Q(1a_2)$	$\delta\Delta Q_\pi$	$\delta\Delta Q_\sigma$	$Q^+(1a_2)$	$\Delta Q(2b_1)$	$\delta\Delta Q_\pi$	$\delta\Delta Q_\sigma$	$Q^+(2b_1)$
2, 3	−3	168	−34	16	147	164	31	−4	188
1, 4	−35	332	3	−63	237	12	−42	74	9
5	50	0	−104	49	−5	262	48	−131	229
6	25	0	164	45	234	386	−26	−9	376

From this result the general conclusion can be drawn that Koopmans' theorem is not always a valid approximation, even in the form (3), *i.e.* as a basis for perturbation calculations. It must fail in particular when, for example, for symmetry reasons, the orbital ψ_J that is vacated by the electron e^- in process (2) is localized only in one part of the molecule M (cf. (8)). According to the assumptions under which Koopmans' theorem was derived [same SCF orbitals ψ_J for M and $M^+(\psi_J)$] first a positive charge increase described by ψ_J^2 will be produced, which is necessarily localized [cf. $M^+(\psi_J)$]. The subsequent relaxation process spreads the positive charge into the region of



(8)

the system where $\psi_J^2 = 0$ [cf. $M_R^+(\psi_J)$]. The resultant charge equalization stabilizes the radical cation (*Pauling*'s electroneutrality rule). If M is substituted in a region where $\psi_J^2 = 0$, then clearly one must take into account the changes $\delta\Delta Q_\pi$ and $\delta\Delta Q_\sigma$ caused by electron relaxation since they give rise to first-order perturbations. Similar considerations apply also to orbitals whose "localization" is not due to symmetry, such as those of "lone pairs". On the other hand, the usual procedures within the framework of Koopmans' theorem may be expected to give reasonable results when ψ_J extends more or less uniformly over the whole molecule M.

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Crystal and Molecular Structure of Cyclooctasulfur Oxide, S_8O[1]

By *Ralf Steudel*, *Peter Luger*, *Hans Bradaczek*, and *Michael Rebsch*[*]

S_8O is formed on condensation of $SOCl_2$ with "crude sulfane" (H_2S_n; $n = 3,4,5\ldots$) by the dilution technique; it crystallizes from CS_2 in yellow needles[2]. We have carried out a single-crystal X-ray structure analysis of such crystals at 10 °C.

The crystals belong to space group $Pca2_1$ with $a = 13.197$, $b = 7.973$, $c = 8.096$ Å, $d_{calc.} = 2.11$, $d_{exp.} = 2.13\ g\,cm^{-3}$. 1008 reflections with θ between 3° and 27° were measured on an automatic Siemens single-crystal diffractometer. 128 reflections whose intensity was less than twice the statistical error were regarded as unobserved. As the substance decomposed gradually the intensity measurements were effected with three different crystals. Scaling was achieved by a reference reflection. We determined the phases by the tangent formula[3]; the structure was refined by the method of least squares with anisotropic temperature factors for all atoms. After convergence of all the parameters the final R value amounted to 5.0%.

Figure 1 shows the result. Table 1 contains the intramolecular nuclear distances and angles. The molecule of S_8O belongs to the point group C_s. The S atoms form a crown-shaped ring in which each set of four atoms lies approximately in one plane. The two planes are almost parallel. The O atom is in an axial position to the ring. The S—O internuclear distance of 1.483 Å corresponds to the value of 1.49 Å calculated from the valence force constant[2].

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Table 1. Bond lengths and angles in the S_8O molecule. Standard deviations in parentheses.

Internuclear distances [Å]					
S^1O	1.483 (0.009)	S^5S^6	2.047 (0.005)	S^7O	3.066 (0.009)
S^1S^2	2.204 (0.004)	S^6S^7	2.071 (0.005)	S^3O	3.096 (0.010)
S^2S^3	2.000 (0.005)	S^7S^8	2.006 (0.005)	S^2O	2.976 (0.010)
S^3S^4	2.064 (0.004)	S^8S^1	2.200 (0.004)	S^8O	2.977 (0.009)
S^4S^5	2.044 (0.005)				

Valence angles [ ]				Dihedral angles [°]			
OS^1S^2	106.0 (0.4)	$S^3S^4S^5$	105.9 (0.2)	$S^1S^2S^3/S^2S^3S^4$	94.8	$S^5S^6S^7/S^6S^7S^8$	93.1
OS^1S^8	106.3 (0.4)	$S^4S^5S^6$	106.7 (0.3)	$S^2S^3S^4/S^3S^4S^5$	102.3	$S^6S^7S^8/S^7S^8S^1$	101.7
$S^2S^1S^8$	101.8 (0.2)	$S^5S^6S^7$	107.9 (0.2)	$S^3S^4S^5/S^4S^5S^6$	107.1	$S^7S^8S^1/S^8S^1S^2$	111.5
$S^1S^2S^3$	102.3 (0.2)	$S^6S^7S^8$	107.4 (0.2)	$S^4S^5S^6/S^5S^6S^7$	98.8	$S^8S^1S^2/S^1S^2S^3$	102.2
$S^2S^3S^4$	108.4 (0.2)	$S^1S^8S^7$	101.6 (0.2)				

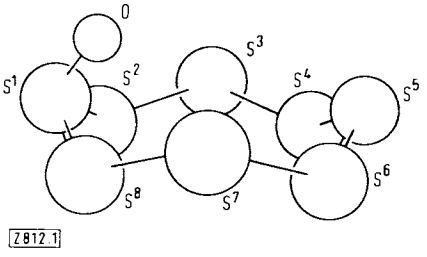
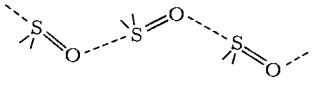


Fig. 1. Structure of the molecule of S_8O.

The intramolecular S—S distances show more pronounced variations than in the S_8 ring of rhombic α-sulfur where they vary between 2.042 and 2.050 Å[4]. Very striking are the two unusually large S—S distances involving the thionyl group (S^1S^2 and S^1S^8: 2.20 Å); these S—S bonds are to be regarded as partial bonds and their ready cleavage probably accounts for the ease of decomposition of S_8O at room temperature. SO_2 and polymeric sulfur are produced in this decomposition[2]; elimination of SO_2 can occur without diffusion or rotation of the S_8O molecule in the crystal since the packing is such that the SO groups of molecules stacked next to and above each other form a planar zig-zag chain:



The unit cell contains two such chains parallel to the *c*-axis. Within each chain the intermolecular S—O distance amounts to 2.935 Å (van der Waals bond length: 3.2 Å); the OSO and SOS angles amount to 175 and 131°, respectively. Such intermolecular interaction of the S_8O molecules was supposed previously on the basis of the IR spectrum[2].

The smallest intermolecular S—S distance of 3.388 Å accords with findings for rhombic sulfur[4] (van der Waals distance: 3.6 Å).

In the S_8O ring the dihedral angles, much discussed in connection with the stability of sulfur rings, vary within relatively large limits. The mean value 101.4°, however, is only slightly greater than that (99°) found for rhombic cyclooctasulfur[5].

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Tetrasulfur Tetranitride—A New Insertion Reagent[**]

By *Herbert W. Roesky* and *Michael Dietl*[*]

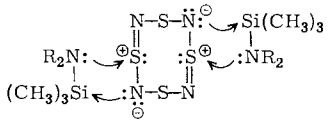
Cleavage of silicon-nitrogen or tin-nitrogen bonds by halides RX has proved to be a versatile synthetic procedure[1,2], but insertion reactions with S_4N_4 have not hitherto been reported.

We have now treated SiN (and also SnN) compounds of type *(1)*[3] with tetrasulfur tetranitride *(2)* in the molar ratio 2:1, and obtained products containing an S_2N_3 skeleton *(3)*, *e.g.*:

$$2\ (CH_3)_3SiNR_2 + S_4N_4 \rightarrow 2\ (CH_3)_3Si{-}N{=}S{=}N{-}S{-}NR_2$$

(1) *(2)* *(3a)*, R = CH_3 : b.p. 29 °C/0.01 torr; *(3b)*, R = C_2H_5: b.p. 37 °C/0.01 torr

The reaction appears to involve nucleophilic attack by the amino nitrogen on a sulfur atom of the S_4N_4 ring, leading to electrophilic cleavage of the metal-nitrogen bond[4].



In this connection particular interest attaches to the reaction of $S_3N_2Cl_2$ *(4)* with SiN compounds. For example, if *(4)* is allowed to react with *(1a)* in the molar ratio 1:2, then S_4N_4 *(2)* is formed as intermediate.

$$4\ (1a) + 2\ S_3N_2Cl_2 \rightarrow (2) + 4\ (CH_3)_3SiCl + 2\ (CH_3)_2N{-}S{-}N(CH_3)_2$$

(4)

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In such circumstances *(2)* exists in a particularly reactive form, being converted completely into *(3a)* by further reaction with *(1a)* according to the first mechanism above.

The compounds *(3)* are intensely red[5], oily liquids that distil unchanged under reduced pressure and react with halides[6].

In its ^{1}H-NMR spectrum, *(3a)* shows the expected two singlets, with intensity ratio 3:2, at $\delta_{(CH_3)_3Si} = -0.33$ and $\delta_{(CH_3)_2N} = -2.93$ ppm relative to $(CH_3)_4Si$ (external). The IR spectrum contains absorptions at 2990 w, 2980 s, 2890 w, 1452 s, 1255 vs, 1187 vs, 1037 w, 962 vs, 850 vs, 760 s, 673 s, 633 s, and 471 w cm^{-1} (capillary between KBr disks). The bands at 2900 are assigned to the C—H stretching and those at 1452 cm^{-1} to the corresponding deformation vibration. The strong bands at 1255 and 1187 cm^{-1} belong to S=N stretching vibrations.

Insertion reactions of S_4N_4 with other organometallic derivatives are at present under study.

General experimental procedure:

$S_3N_2Cl_2$ (0.05 mol) or S_4N_4 (0.1 mol) is suspended or partly dissolved, respectively, in CH_2Cl_2 contained in a two-necked flask with an attached dropping funnel and reflux condenser. $(CH_3)_3SiNR_2$ (0.2 mol) is added dropwise to this mixture at a rate such that the methylene chloride just boils. At the end of the reaction the solvent is removed and the product distilled at oil-pump vacuum. The reaction gives an almost quantitative yield of *(3)*[7].

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German version: Angew. Chem. 85, 453 (1973)

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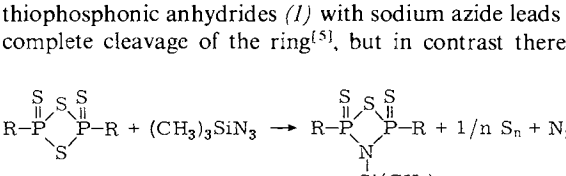
[7] The composition of the compounds *(3)* was proved by complete elemental analysis.

A Novel Covalent Azide Reaction in Phosphorus Chemistry[**]

By *Herbert W. Roesky* and *Michael Dietl*[*]

The best known reaction of azides for preparation of phosphazenes is connected with the names *Staudinger* and *Horner*: it consists in treating phosphane derivatives with alkyl, aryl, or acyl azides[1–4]. Reaction of cyclic alkyldithiophosphonic anhydrides *(1)* with sodium azide leads to complete cleavage of the ring[5], but in contrast thereto



(1) *(2)*

(3a), R = CH_3: m.p. 114 °C
(3b), R = C_2H_5: oil

heterocycles of type *(3)* are formed quantitatively from trimethylsilyl azide *(2)* and *(1)*.

The removal of sulfur and nitrogen begins already at room temperature and no further nitrogen is evolved if an excess of *(2)* is used.

(3a) is colorless, sublimes, and can be unambiguously identified by means of its ^{1}H-NMR and mass spectrum[6]. For the $(CH_3)_3Si$ group the ^{1}H-NMR spectrum shows a singlet at $\delta = -0.53$ ppm and for the CH_3P groups a doublet at $\delta = -2.52$ ppm with $J_{HCP} = 14.5$ Hz [relative to $(CH_3)_4Si$, external; solution in CH_2Cl_2]. In the mass spectrum the following characteristic fragments can be seen as well as the molecular ion 275 (58%): *m/e* = 260 [67%; $M-CH_3$], 245 [1%; $M-2CH_3$], 228 [3%; $M-SCH_3$], 211 [7%; $M-2S$], 196 [10%; $M-S_2CH_3$], 182 [5%; $(CH_3)_3SiNPS_2$], 170 [12%; $(CH_3)_2P_2S_2N$], 164 [10%; $(CH_3)_3SiNP_2CH_3$], 150 [100%; $(CH_3)_3SiNPS$], 138 [10%; $(CH_3)_2P_2SN$], 118 [26%; $(CH_3)_3SiNP$], 73 [62%; $(CH_3)_3Si$] 63 [11%; PS], 45 [20%; PN], and 32 [65%; S].

The IR spectrum of *(3a)* (KBr disk) shows bands at 2970 w, 2910 w, 1398 vs, 1300 vs, 1295 vs, 1286 s, 1255 vs, 985 vs, 910 vs, 845 vs, 770 vs, 758 vs, 700 vs, 620 vs, 541 s, 430 vs, 412 vs, 340 s, and 320 w cm^{-1}. It differs from the spectrum of *(1a)* particularly in the region of the (HCSi) deformation vibration.

Experimental:

$(CH_3)_3SiN_3$ (11.5 g, 0.1 mol) is added dropwise with stirring to a suspension of $(CH_3PS_2)_2$ (22 g, 0.1 mol) in CH_2Cl_2 (300 ml). Vigorous gas evolution sets in at once. At the end of the reaction the mixture is warmed for a short time and then filtered from the deposited sulfur under nitrogen. The solvent is removed in a vacuum and the residue is either recrystallized from CCl_4 or sublimed at oil-pump vacuum. The yield is quantitative (27 g).

Received: March 9, 1973 [Z 815b IE]
German version: Angew. Chem. 85, 454 (1973)

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Chemiluminescent Paracyclophanes[**]

By *Karl-Dietrich Gundermann* and *Klaus-Dieter Röker*[*]

Some time ago, *White et al.*[1] synthesized chemiluminescent compounds of type *(1)* containing a hydrazide group in a part of the molecule that is not itself luminescent or at most slightly so; the electronic excitation energy produced by their oxidation is transferred to another part of the same molecule that fluoresces strongly in the visible region; *(1)* chemiluminesces with the fluorescence emission of *N*-methylacridone. That the energy transfer is *intra*-molecular is shown, *inter alia*, by the fact that a mixture of

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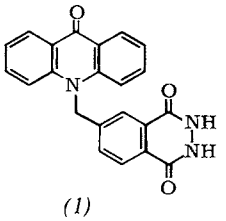
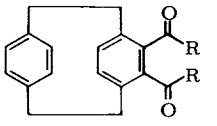
[**] Constitution and Chemiluminescence, Part 5.— Part 4: [5].

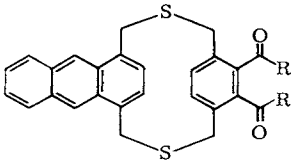
phthalhydrazide and *N*-methylacridone does not emit under the same conditions.



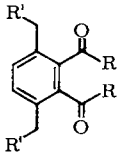
(1)



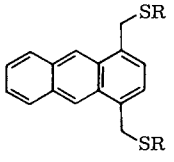
(2), -R R- = -NH-NH-
(3), R = OCH_3



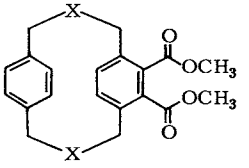
(4), -R R- = -NH-NH-
(5), R = OCH_3



(6), R = OH, R' = H
(7), -R R- = -NH-NH-, R' = H
(8), R = OCH_3, R' = Br



(9), R = H
(10), R = CH_3



(11), X = S
(12), X = SO_2

The methylene group in *(1)* and similar compounds precludes mesomeric interaction between the energy-producing and the emitting parts of the molecule; the two partial structures cannot assume the parallel positions particularly favorable for energy transfer (cf. [2]). Considerable parallel fixation between the phthalhydrazide and the fluorescing group should, however, be present in the corresponding paracyclophanes.

We have synthesized [2.2]paracyclophane-4,5-dicarboxylic hydrazide *(2)* and 2,15-dithia[3.3](1,4)anthraceneparacyclophane-18,19-dicarboxylic hydrazide *(4)* by *Vögtle*'s method[3]. In both these compounds the hydrazide portion resembles an ω,ω'-disubstituted derivative of 3,6-dimethylphthalic acid *(6)*, whose hydrazide *(7)* shows no chemiluminescence on hemin-catalyzed oxidation by aqueous alkaline hydrogen peroxide and extremely little in the system DMSO/*tert*-butoxide/oxygen. In *(4)* a substituted 1,4-bis(mercaptomethyl)anthracene *(9)* acts as a group that fluoresces in the visible region.

(4) (5.1×10^{-4} mol/l) chemiluminesces on oxidation by oxygen/potassium *tert*-butoxide (2.3×10^{-2} mol/l) in dimethyl sulfoxide at $\lambda_{max} = 450$ nm [fluorescence of *(10)*: 423 nm] with about double the amount of light emitted by 2,3-anthracenedicarboxylic hydrazide[5]. A mixture of *(10)* and the hydrazide *(7)* emits only about 1/25 as much light as *(4)* under the same conditions.

The paracyclophane derivative *(2)* fluoresces although formally only a *p*-xylene residue that cannot fluoresce is present as acceptor of excitation energy: *Vala*, *Haebig*, and *Rice*[2] previously noted the ability of unsubstituted [2.2]paracyclophane to fluoresce ($\lambda_{max} = 355$ nm). The emission of *(2)* in the system DMSO/*tert*-butoxide/oxygen ($\lambda_{max} = 395$ nm) is considerably weaker than that of *(4)* but nevertheless exceeds that of *(7)* in the same system by an order of magnitude.

(2) was obtained by conversion of disodium *p*-phenylenedi(methanethiolate) by *(8)* into *(11)* by the dilution method[3] (yield *ca.* 30%; m.p. 147 °C), oxidation of *(11)* by acetic acid/perhydrol to the disulfone *(12)* [yield 65%; m.p. 320 °C (dec.)], pyrolysis of *(12)* to *(3)* (yield 25%; m.p. 100 °C) and reaction of *(3)* with hydrazine hydrate in methanol. When heated, *(12)* affords only traces of *(3)* (cf. [4]); only the addition of a 12-fold amount of *p*-terphenyl, which clearly exerts a matrix-like short-range ordering effect, leads to yields around 25% of *(3)* on pyrolysis at 325 °C [*(3)*: ^{1}H-NMR ($CDCl_3$), $\tau = 6.50$—7.20 (m, benzyl-H) 3.32, 3.43 (phenyl-H), and 2.92 (phthalyl-H)].

We obtained *(4)* analogously. Simultaneous dropwise addition of *(8)*, *(9)*, and sodium hydroxide to a large volume of ethanol gave *(5)* (yield 31%; m.p. 230 °C) whose reaction with hydrazine led to *(4)*. We have not yet succeeded in oxidizing *(5)* to the disulfone. *(5)*: ^{1}H-NMR ($CDCl_3$), $\tau = 5.69$—6.05 (m, benzyl-H), 3.09, 2.23, 1.48 (anthracenyl-H), and 3.56 (phthalyl-H). This shift to higher field in comparison with the phthalyl protons of *(3)* proves the presence of the *anti*-isomer (cf. [6]).

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Macromolecular Colloquium

The Macromolecular Colloquium—arranged by the Institut für makromolekulare Chemie der Universität Freiburg—was held at Freiburg/Br. (Germany), March 8—10, 1973.

From the lectures:

Polymerization Induced by Field Ionization and Field Emission in Various Liquid Monomers

By *Marcel Brendle*[*]

It was recently shown that polymerization reactions in bulk can be brought about purely by the action of very high electric fields, with no catalyst[1].

The ions or radical-ions are formed by field emission or field ionization of the monomer. This reaction requires very high electric fields ($>10^6$ V/cm). The most frequently used electrode system consists of a fine tungsten tip and a flat polished counterelectrode with an electrode separation d of 0.5 cm and an applied voltage V of 30 kV. Depending on the polarity of the tip, cationic, anionic, and in most cases also free-radical polymerizations can be initiated.

Since the currents are limited to an order of a few μA, very low concentrations of water or other deactivating impurities are sufficient to prevent ionic polymerization. In fact, a current of 1 μA for one hour corresponds to only 3.74×10^{-8} mole, *i.e.* 7×10^{-7} mole of water in a volume of 50 ml.

Ionic polymerizations can therefore occur only in very carefully dried monomers. There are probably no counterions; the lifetime of the ions is probably no greater than the time taken to migrate from one electrode to the other.

On the basis of this view, we have shown that the Faraday yield

$$R_F = \frac{\text{quantity of polymer formed}}{\text{quantity of charge introduced}}$$

should be

$$R_F = k_p m \frac{d^2}{\mu V} M$$

k_p = growth constant, m = concentration of monomer, M = molecular weight of monomer, μ = migration velocity of the ions.

In the case of styrene, we were able to show that the voltage V and the distance between the electrodes d correspond to this equation if the influence of the water that is always present is taken into account.

To determine the ratio of the ions deactivated by impurities to the electrically discharged ions, we compared the lifetimes of the growing ions τ_p to the time of migration τ_m. μ was determined by two independent methods[2].

In the cationic polymerizations of styrene, of cyclopentadiene, and of isobutyl vinyl ether, the τ_p and τ_m values agree to some extent.

Ultradry monomers (obtained by the method of *F. Williams* and *D. Metz*) and a more accurate determination of the migration time are necessary for the satisfactory determination of the constant k_p for ionic polymerizations without counterions. Experiments with this purpose are in progress.

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Determination of the Configuration of Polybutadienes and Poly-α-methylstyrenes by ^{13}C-NMR Spectroscopy

By *K.-F. Elgert* (lecturer), *H.-J. Cantow*, *B. Stützel*, and *P.-J. Frenzel*[*]

High-resolution ^{1}H-NMR spectroscopy allows the determination of the tacticity of poly-α-methylstyrenes from the resonances of the methyl group, and independently also from those of the *o*-phenyl protons on deuteration of the *p* and *m* ring protons. A variation of the tacticity with the molecular weight has been detected in this way in products obtained by anionic polymerizations with butyllithium in THF[1]. In polybutadienes, on the other hand, the *cis*-1,4 and the *trans*-1,4 resonances are situated close together and are difficult to separate while no tacticity effect can be detected in the 1,2 sequences[2]. This invariance of the spectra with respect to the configuration of the 1,2 units allowed the quantitative analysis of the succession of chemically different sequences in α-methylstyrene-butadiene copolymers from proton resonance spectra[3].

On the other hand, the ^{13}C-NMR spectra found for polybutadienes at 22.7, 25.2, and (with a superconducting system) 67.9 MHz are satisfactorily resolved with regard to *cis*-1,4 and *trans*-1,4 resonances and the tacticity of 1,2 linkages. By measurements on products obtained by various polymerization mechanisms, it was possible to show from the resonances of the ^{13}C nuclei of the vinyl and aliphatic resonance region that the positions of the signals are influenced not only by the different isomeric structural units but also by their neighboring groups. Investigations on the isomerization of *cis*-1,4-polybutadienes were also included in the discussion.

Determination of configurational sequences is also possible in poly-α-methylstyrenes. The dependence of the tacticity

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of anionic products on the molecular weight as found by ^{1}H-NMR measurements can be confirmed in this way.

[1] Makromol. Chem. *145*, 95 (1971).
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[3] Makromol. Chem., in press.

Asymmetric Stereoselective Polymerization of the *N*-Carboxy Anhydrides of D,L-Leucine

By *Heinrich G. Bührer* and *Hans-Georg Elias* (lecturer)[*]

N-Carboxy-D,L-leucine anhydride was polymerized in dioxane, benzene, tetrahydrofuran, butanone, or dimethylformamide between 10 and 55 °C with 15 primary and secondary amines as initiators. The optical yield of polymer can be satisfactorily described for conversions between 3 and 94% by an ideal copolymerization equation

$$d[L]/d[D] = R([L]/[D])$$

The highest R (= 1.30) was found for initiation with L-proline methyl ester in dioxane at 25 °C. The ideal copolymerization equation can be derived for ten models, depending on the assumptions regarding homopropagation, heteropropagation, homo-absorption, and/or hetero-absorption. The most likely answer, according to all the observations, is a pure or at least strongly predominant homopropagation ($k_{LL}=k_{DD}$; $k_{LL}[P_L^*] \gg k_{DL}[P_D^*]$ and $k_{DD}[P_D^*] \gg k_{LD}[P_L^*]$), with a constant concentration of active chain ends in the D and in the L configuration ($[P_L^*]=$ const.; $[P_D^*]=$ const'.; $[P_L^*]/[P_D^*] \neq 1$).

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Supports Containing Diazonium Groups for Biologically Active Compounds

By *J. Exner* (lecturer), *M. Křiváková*, *J. Labský*, *M. Bleha*, *O. Wichterle*, and *J. Čoupek*[*]

Suspension copolymerization of hydrophilic monomers with a comonomer that contains a primary amino group leads, in an inert solvent in the presence of a crosslinking agent, to macroporous aerogels having well-defined pore size distributions and with large internal surface areas. These properties allow the use of the copolymers as supports for biologically active compounds for catalytic processes and for affinity chromatography. The biologically active component is covalently bonded to the surface of the highly crosslinked matrix.

Because of the physical properties of the gel, the support possesses outstanding mechanical strength and good flow-through properties with minimal non-specific adsorption.

The relations between the properties of the support skeleton, the diazotization conditions, and the concentration of diazonium groups and their reactivity with passive coupling components, model amino acids, and model enzymes have been followed. At the same time, the influence of the modifying reactions on the physical structure of the gel and the influence of the unreacted ionic groups on the activity of the bound enzyme were studied. Possible applications of these macroporous hydrophilic supports based on hydroxyalkyl methacrylate were discussed.

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Plant Structural Polysaccharides: Structure and Biosynthesis

By *W. W. Franke* (lecturer) and *W. Herth*[*]

The characteristic morphology of plant cells and tissues is determined by the cell wall, and in particular by the structural polysaccharides. The latter are characterized by their mechanical stability, their high degree of polymerization, their fibrillar superstructure, and their chemical stability (in particular toward alkalis).

Over the past decade, it has been shown that in addition to the typical representatives of this group (cellulose and chitin) some other polysaccharides are also capable of fulfilling these functions. These polysaccharides include β-1,3-glucans, β-1,3-xylans, β-1,4-mannans, and also xyloglucans, glucomannans, and glucogalactans. The algae in particular show wide variations in this respect. In some cases it has been possible to demonstrate that the membrane-bound biosynthesis of these polymers occurs not outside but inside the cells, in the sacs of the Golgi complex, the polymeric product being released from the cell by membrane fusion processes taking the form of exocytosis. In the course of such a secretion even the crystallization stage can take place intracellularly.

Chemical analyses show that such structural polysaccharide fibrils are not pure polyglycans, but contain a stable and probably covalently bound peptide portion with a very characteristic pattern of amino acids (in particular, a high proportion of OH-amino acids). It has recently been suggested that this peptide portion may have a particular significance in controlling the synthesis of structural polysaccharides, and the analogies to the formation of animal and bacterial peptidoglycans and the more alkali-labile cell-wall substances are emphasized.

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Kinetic and Morphological Studies on the Free-Radical Grafting of Styrene on Polybutadienes

By *J. P. Fischer*[*]

The kinetics of the free-radical grafting of styrene on polybutadienes is investigated with the aid of fractional precipitations. It is possible in this way to describe the dependence of the nature and quantity of the graft copolymers formed on the structure of the polybutadienes and the conditions of the thermal and initiated polymerization of styrene.

Kinetically derived equations allow the separation of the grafting into the polymer-radical and initiator-radical contributions. Different initiators give very different grafting reactivities. Thermal graft polymerization shows only a polymer-radical contribution, which increases in particular with the 1,2 vinyl content of the polybutadiene and with rising temperature.

The length of the grafted chains is determined by the kinetics of the styrene polymerization, and can be adjusted

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particularly readily by chain transfer agents. The average number of grafted chains per grafted polybutadiene molecule increases from a value of 1 with increasing monomer conversion in a manner that can be described kinetically.

The influence of the nature and quantity of the graft copolymer on the adjustment of the morphology in the graft polymerization of styrene on polybutadiene is determined independently of the normally coupled effects, *e.g.* of the viscosity of the polystyrene matrix, by experiments with additions of graft copolymer. Within certain molecular weight limits, the emulsifier effectiveness is proportional to the length of the grafted chain. Consequently, the graft efficiency (% of grafted styrene with respect to total polystyrene) is found to be a good combination measure for describing the effect of graft copolymers on the dispersity of the multiphase system in question.

A Method for the Investigation of Stress-Induced Rearrangement Processes in Polymers: Crystal Transition II to I of Poly-1-Butene by Mechanical Stresses

By *G. Goldbach*[*]

The rate of transition of the tetragonal modification II of poly-1-butene into the hexagonal crystal form I can be considerably increased by mechanical stresses. Investigations on the stress-induced crystal transition II to I over a wide temperature range showed that a noticeable transition begins only when the yield stress is reached (uniaxial tensile tests). Since the yield stress corresponds essentially to the shear strength of the material, one could assume that the transition from modification II to modification I is induced by shear stresses rather than by tensile stresses. Measurements were carried out in a multiaxial stress field to establish which stress component is decisive for the transition.

The experimental arrangement chosen was a film with a hole (modification II) under tensile stress, from whose geometry the stress fields can be calculated from elasticity theory. The degree of transition from II to I was measured by IR spectroscopy along specific lines at the edge of the hole where the maximum shear and principal stresses are known. The evaluation of the results showed that in tensile tests the II to I-transformation is induced by a tensile deformation of the crystals and not by a shear deformation.

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Polymeric Reagents

By *M. L. Hallensleben*[*]

The use of polymeric reagents instead of low molecular weight reagents in preparative organic chemistry offers a number of important advantages. Linear polymeric reagents can be easily separated from the product after a reaction because of the difference in solubility in certain solvents; crosslinked polymeric reagents considerably simplify the isolation of products from the reaction mixture[1, 2]. Use in a column considerably increases the yields in many cases, since the substrate in the column always follows a large concentration gradient of the reagents.

Investigations were carried out on a number of polymeric reagents that satisfy the essential conditions for economical use of such compounds. These conditions are that reactions on the reagents should proceed polymer-like, so that there is no loss of the above advantages as a result *e.g.* of chain degradation, and in particular there is no change in the flow properties in a column in the case of gels; polymeric reagents must be capable of being regenerated, since their synthesis is generally more expensive than that of low molecular weight analogs.

These conditions are satisfied by poly-*p*-styryl iodide chloride[3, 4] and by poly-*p*-iodosostyrene diacetate[4, 5], which can be used for chlorinations[6] and for oxidations and acetylations[7] respectively. The use of poly-*p*-vinylbenzoyl chloride and of poly-4-vinylpyridinium tetrahydridoborate as polymeric reagents was also studied. From the above points of view, the only polymeric metalating agents that can be used and regenerated are those with complexed metal.

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[1] *W. Heitz* and *R. Michels*, Makromol. Chem. *148*, 9 (1971).
[2] *W. Heitz* and *R. Michels*, Angew. Chem. *84*, 296 (1972); Angew. Chem. internat. Edit. *11*, 298 (1972).
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Use of Polymerization Kinetics for the Investigation of Homogeneous Catalytic Processes

By *G. Henrici-Olivé* (lecturer) and *S. Olivé*[*]

The activation of molecular oxygen on soluble transition metal centers is a topic of current interest. On the one hand, low molecular weight model substances should help to provide an understanding of the processes that occur on the respiratory pigments, while on the other it is hoped that access will be gained to selective oxidation of suitable substrates with homogeneous catalysis.

We investigated cobalt complexes of the general form $X_2R_4Co(II)$ (X = organic anion, R = primary aliphatic amine), which eagerly take up oxygen to form diamagnetic μ-peroxo complexes: $X_2R_3Co—O—O—CoR_3X_2$. The latter decompose when heated, with formation of a paramagnetic Co(II) species, which is again able to take up oxygen (catalysis), and with oxidative modification of amine ligands.

The thermal decomposition of the complexes leads to free radicals that initiate the polymerization of styrene. From the kinetics of the polymerization, it was possible to calculate the decrease in the concentration of the radical-producing species with time. The magnetic changes in the system also allowed direct kinetic investigation of the decomposition of the μ-peroxo complex. A first-order course was found in both cases, with equal rate constants. This shows that the free radicals are formed in connection with the decomposition of the complex.

The reaction products of the amines suggest the intermediate occurrence of alkyl free radicals.

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Ring-opening Polymerization of Cycloolefins in the Presence of Metathesis Catalysts

By *Hartwig Höcker* (lecturer), *Rüdiger Musch*, *Frank R. Jones*, and *Ingo Lüderwald*[*]

The metathesis reaction of acyclic monoolefins leads to transalkylidenation products, whereas cyclic olefins react by the same mechanism to give oligomers and polymers which should have a cyclic structure.

To allow the conclusive demonstration of the cyclic structure of these oligomers, the reaction conditions were optimized for the oligomerization of cyclooctene and the oligomers up to the decamer were separated by gel permeation chromatography and investigated spectroscopically. The IR, the NMR, and particularly the mass spectra which show the molecular ion peak of the oligomer in question, up to the nonamer, with a peak-free field in front, confirm the cyclic structure.

The catalyst for the reaction consists of a transition metal halide, an activator in certain cases, an alkylating or a reducing agent, and an aluminum halide. In particular, the systems $WCl_6/C_2H_5OH/C_2H_5AlCl_2$, $WCl_2(OC_6H_5)_4/BuLi/AlBr_3$, and $WCl_6/BuLi/AlBr_3$ were investigated. The results of the polymerization of cyclooctene in the presence of the systems mentioned lead, with consideration of the yield and the structure of the polymers obtained, to the following conclusions:

1. An activator is necessary only if a relatively weak alkylating agent is used.

2. Two ligands of the transition metal are replaced by alkyl groups.

3. An aluminum halide is required as a complexing agent.

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Quaternary Structure and Activity of Enzymes

By *Rainer Jaenicke*[*]

The definition of the quaternary structure of enzymes contains implicitly the assumption of inactive subunits according to the reaction

$$M_n \text{ (active)} \rightleftharpoons n \cdot M \text{ (inactive)}.$$

This correlation of quaternary structure and activity cannot be understood from the point of view of evolution, since association is preferably considered to cause *regulation* rather than causing *activity* itself.

Normally, determinations of particle weight and of enzymatic activity are carried out in concentration ranges differing widely from each other. On carrying out a systematic study of the particle weight of some glycolytic enzymes under conditions identical to those used in the enzymatic test ($c \leqq 1$ µg/ml), the correlation of molecular weight and activity to the parameters of the solution turns out to be different for different enzymes. In general conditions which lead to complete splitting into subunits concomitantly cause deactivation. This effect can be accounted for by denaturation (without dissociation), since denaturation in general precedes dissociation.

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In the case of lactate dehydrogenase the concentration-dependent reactions of dissociation and deactivation run parallel; at the same time, the kinetics of reassociation after dissociation and deactivation at pH < 3 are shown to be slow in comparison with the kinetics of renaturation[1].

The apoenzyme of glyceraldehyde-3-phosphate dehydrogenase occurs in a partially dissociated state under standard conditions of the enzymatic test; depending on the concentration, dissociation gives both dimers and monomers. In the presence of the coenzyme (NAD) the equilibrium is shifted to the tetrameric state.

In the case of aldolase, splitting in 8 M urea and subsequent reactivation by dialysis or dilution points to active subunits[2]; in this case decreasing protein concentration as well as increasing ionic strength do not lead to dissociation under any conditions of the experiment.

It may thus be concluded that under certain circumstances subunits are capable of showing enzymatic activity. Basically, the enzyme is stabilized by association, just as it is by coenzyme binding. Under the conditions *in vivo* the enzymes under consideration should be regarded as associated, since even in the case where the effective concentration of the enzyme is low, other proteins or polyelectrolytes inhibit dissociation as well as deactivation.

[1] *A. Levitzky*, FEBS Letters *24*, 301 (1972).
[2] *W. Chan*, Biochem. Biophys. Res. Commun. *41*, 1198 (1970).

International Molecules

By *Rolf Hosemann*[*]

Interesting, novel, rubbery-elastic phenomena have been observed for linear and branched polyethylenes; these phenomena allow conclusions to be drawn regarding the molecular structure, and appear to be typical for a large class of synthetic and biological linear high polymers.

In the case investigated, necking on drawing leads to a drawing factor that is characteristic of the material. If the material is subsequently crosslinked with small doses of radiation (*e.g.* 15 Mrad of ^{60}Co) and then maintained not too high above its melting point for not too long, the original form is restored in every detail, down to colloidal dimensions. Large-angle and small-angle X-ray studies show that the original crystal structure of the material crystallized from the melt was completely altered on drawing. The "memory" lies in the "international" molecules, which join these individual crystal regions that are distorted and deformed in the drawing process.

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Properties of *N*-Chloro-polyamides

By *B. U. Kaczmar*[*]

A number of chemical and physicochemical properties of certain *N*-chloro-polyamides allow the preparation of a resin whose high oxidation potential can be used for oxidation reactions in the aqueous phase. These properties include:

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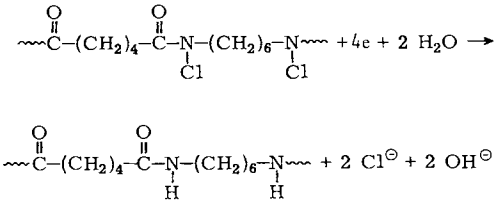
1. the oxidative action of *N*-chloro-polyamides, *e.g.* N—Cl-nylon 66:



Numerous organic and inorganic substances can be oxidized in accordance with this scheme. The substances whose standard potentials are known can be arranged in order of increasing potential up to the system:

$$Br_2 + 2e \rightleftarrows 2Br^{\ominus}$$

2. The *N*-chloro-polyamide is reduced in accordance with the above redox equation to the polyamide, from which the oxidizing agent can be regenerated by *N*-chlorination. An aqueous solution of HOCl is very suitable for use as the *N*-chlorinating agent.

3. Various methods can be used to bring the *N*-chloro-polyamide into a favorable form for the kinetics of a heterogeneous redox reaction in aqueous systems. We polymerized *N*-substituted acrylamides into ion exchange resins and obtained a snake-cage configuration. After *N*-chlorination, products of this type can exert an oxidizing action and can exchange ions to a greater or lesser extent, depending on the starting substances.

The Quasi-Static Elasticity Moduli of Semicrystalline Copolymers of Ethylene

By *H. G. Kilian* (lecturer) and *D. Klattenhoff*[*]

The elasticity moduli of random copolymers of ethylene at 1 Hz were measured as a function of the temperature and of the composition of the copolymers. From knowledge of the main superstructure parameters of the semicrystalline systems, and taking energy-elastic and entropy-elastic contributions into account, we calculate moduli that are determined by "crystal crosslinking" and by "physical" crosslinking in the noncrystalline regions. The theoretical elastic properties of systems with different degrees of crystallinity depend on the model used. Characteristics of the superstructure must be taken into consideration.

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Partial Miscibility of Polymer Solutions

By *R. Koningsveld* (lecturer) and *W. H. Stockmayer*[*]

If a polymer solution separates into two liquid phases, one of these phases is usually extremely dilute, while the other is relatively concentrated. Extensive thermodynamic studies have been carried out on the latter state, in which the macromolecular coils overlap considerably, as well as on the dilute solution, in which the coils are separated from one another by regions of pure solvent.

To describe such phase equilibria, one requires an expression for the free enthalpy of mixing, which covers the two concentration ranges continuously. A suitable semi-empirical equation is proposed, which has the advantage of containing no additional adjustable parameters. The values of the parameters can be found from independent experimental data on dilute and on concentrated solutions.

It is shown that this function can at least partly explain the discrepancy found by *Breitenbach* and *Wolf*[1] in certain phase relations in the polystyrene-cyclohexane system. The effect of the dilute solution is generally evident only to a small extent in the phase separation.

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[1] *J. W. Breitenbach* and *B. A. Wolf*, Makromol. Chem. *108*, 263 (1967).

Determination of the Radius of Gyration of Polymethylmethacrylate in the Vitreous State by Neutron Diffraction

By *R. G. Kirste*, *W. A. Kruse* (lecturer), and *J. Schelten*[*]

Light diffraction and X-ray diffraction yield little information regarding the morphology of filament molecules in the pure, amorphous phase. A new procedure has been devised for this purpose. Dilute solid solutions of the normal polymer in the fully deuterated polymer are prepared. Because of the large difference between the coherent scattering cross sections of D and of H, the neutron diffraction experiments can be evaluated in the same way as light diffraction and X-ray diffraction experiments on dilute solutions of polymers in low molecular weight liquids. As the background, one subtracts the scattering of a polymer preparation containing D and H in the same ratio as the solid solutions, but with the protons and the deuterons randomly distributed over all the molecules.

The method was first used for the investigation of vitreous polymethyl methacrylate (PMMA). The specimens were prepared by dissolution of the calculated quantity of a fractionated normal PMMA (*i.e.* a PMMA containing protons) in deuterated monomeric MMA and subsequent polymerization of the deuterated monomer. Equilibration is ensured by annealing at 130 °C. For $M_w = 250000$, one obtains a Zimm plot, from which the second virial coefficient of the osmotic pressure was found to be $A_2 = 0$ and the radius of gyration to be $r_z = 130$ Å ($r_w = 116$ Å). The radius of gyration is almost the same as in a low molecular weight θ-solvent.

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The Deformation of Single Spherulites

By *M. Kryszewski*[*]

In a number of articles we have discussed the deformation of single spherulites and considered several inconsistencies

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in the literature in this connection. Our theory dealt with the deformation of two-dimensional spherulites; a flat, two-dimensional structure consisting of radially distributed two-dimensional individual elements with a definite anisotropy of the mechanical properties was assumed.

This model was then extended to a three-dimensional spherulite, which consists of two-phase volume elements with transverse anisotropy of the mechanical properties in the radial direction. On the assumption of a definite distribution of the mechanical stress, the deformation of these individual volume elements can be calculated. By summation of their translation, it is possible to calculate the dimensions of spherulites deformed by external mechanical forces. These results can be compared with direct results from optical microscopy. The distribution density of the structural elements in the deformed spherulite was also calculated and taken into account in the theory of small-angle light scattering by spherulites (*Samuels* approximation).

Determination of the Lengths of Grafted Chains and Incompatibility of Graft Polymers

By *Rainer Kuhn* (lecturer), *Heiner Alberts*, and *Herbert Bartl*[*]

The molecular weights M_w of the grafted chains in graft polymers and the incompatibility of the grafted chains with the backbone polymer can be determined by light-scattering measurements in solution if the solvent used in these measurements is isorefractive with the backbone polymer and if the content of grafted chains by weight is known.

The method is illustrated for fractions of graft polymers in which styrene is grafted on ethylene-vinyl acetate copolymer. From the anomalous Zimm diagrams at 90 °C in toluene, which is isorefractive with ethylene-vinyl acetate copolymers at this temperature, almost regardless of the vinyl acetate content, one obtains the molecular weights M_w of the grafted polystyrene chains if one molecule contains only one grafted chain, irrespective of whether ungrafted backbone polymer is still present.

The anomalous Zimm diagrams also provide a measure of the incompatibility of the grafted chains with the backbone polymer, both through the virial coefficients and through the radii of gyration of the grafted chains. Also from the anomalous Zimm diagrams, it is possible to define a θ concentration at which the length of the grafted chains M_w can be determined by light scattering at only one concentration.

After calibration, the molecular weight of the grafted chain can be deduced simply from the phase separation determined by turbidimetric measurements.

By combination of light-scattering and phase-separation measurements for molecules having more than one grafted chain per molecule, it is possible to estimate the molecular weights and the number of grafted chains per molecule.

After suitable fractionation, the chain-length distribution of the grafted chains in graft polymers can also be obtained by the light-scattering method described.

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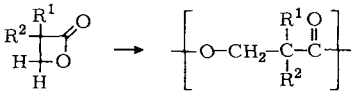
Preparation, Structure and Mechanical Properties of Block Copolyesters from β-Lactones

By *R. W. Lenz*[*]

The ring-opening polymerization of two 2,2-dialkyl-β-propiolactones to form linear polyesters (initiated by ammonium carboxylates) was studied:



PL, $R^1 = R^2 = CH_3$
MPL, $R^1 = CH_3$, $R^2 = n\text{-}C_3H_7$

Initial investigations on the polymerization of MPL showed that this anionic polymerization reaction formed polymers having very narrow molecular weight distributions, indicating the existence of a "living polymer" system. As a result, AB and ABA block copolymers of PL (as the A unit) and MPL were prepared and characterized for crystallinity, melting point, and stress-strain properties as films. Unusual crystallinity and melting point behavior was observed by DSC in both the block copolymers and the MPL homopolymers, and both PL and MPL polyesters are believed to exist in interchangeable helix and linear zig-zag crystalline unit cells (possibly as a function of elongation) as indicated by X-ray diffraction studies. The tensile properties of the ABA block copolymers were believed to be dependent upon the quality of phase separation between PL and MPL blocks. Phase separation behavior was investigated by dynamic-mechanical methods.

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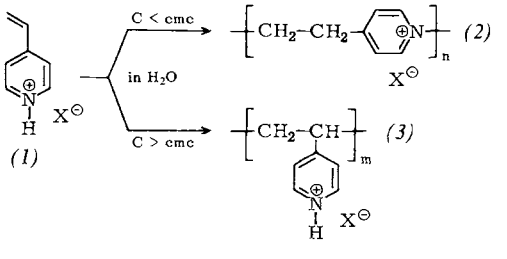
Polymerization Reactions of 4-Vinylpyridinium Salts in Aqueous Solutions

By *Volker Martin* (lecturer), *Helmut Ringsdorf*, *Helmut Ritter*, and *Wolfgang Sutter*[*]

The "spontaneous" polymerization of 4-vinylpyridinium salts *(1)* in water leads to polymers having different structures according to the monomer concentration. The change of product is explained by aggregation of the monomers *(1)* above the critical micelle concentrations (cmc). Polyadducts *(2)* are formed below these concentrations by a nucleophilic addition reaction, and polymers *(3)* at higher concentrations, probably by a free-radical mechanism.



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The critical micelle concentrations (cmc) of 4-VP salts are strongly dependent on the counterion. They can be lowered by addition of foreign salts. At the same time, the "critical polymerization concentrations" (cpc), the concentrations at which polymer formation starts, are also lowered.

Mixtures of *(2)* and *(3)* are found in the region of the critical micelle concentrations. The width of the transition range increases with decreasing tendency for the monomer to form micelles.

The effects of CO_2, SO_2, O_2, and NO on the polymerization behavior below and above the critical micelle concentration were investigated. Anionic (CO_2) and free-radical (O_2, NO) inhibitors have no influence on the formation of the polyadduct *(2)*. The formation of the polymer *(3)*, on the other hand, is strictly inhibited by O_2 and NO.

Light-Induced and Free-Radical Initiator-Induced Cationic Polymerization of *N*-Vinylcarbazole in the Presence of CBr_4

By *O. F. Olaj* (lecturer), *J. W. Breitenbach*, and *H. F. Kauffmann*[*]

On irradiation ($\lambda = 365$ nm) or addition of azobisisobutyronitrile (AIBN) to a benzene solution of *N*-vinylcarbazole (NVC) and CBr_4, a rapid polymerization begins. The conversion-time curves have a sigmoid shape in every case; termination processes are of minor importance at least in the light-induced polymerization, since after the light source is switched off, the polymerization continues for a long time at the rate prevailing at this instant. The polymerization is brought to a stop only by a side reaction with formation of a colored substance or by exhaustion of the monomer.

A kinetic approach, that is based on the absence of a termination reaction and takes into account the consumption of monomer as the reaction proceeds, leads to the equation

$$-\ln(1-U) = Kt^2$$

(U = conversion in fractions, t = reaction time)

which is excellently satisfied by the experimental data. The composite quantity K in the photo-initiated polymerization is proportional to $I^{\frac{1}{2}}$ at low intensities I, and to I at high intensities; no equivalent trend with respect to the initiator concentration can be detected for the AIBN-initiated polymerization, for which K is roughly proportional to $[\text{AIBN}]^{0.75}$.

The termination-free character of the polymerization points to an ionic mechanism; in copolymerizations with styrene or methyl methacrylate as comonomers, NVC is almost exclusively incorporated into the polymer. This is typical of a cationic polymerization mechanism.

The cationic character of the AIBN-initiated polymerization can be explained by the assumption that the free radicals formed by decomposition of the initiator are converted after a few free-radical growth steps into 1-bromo-1-carbazylalkyl structures by transfer reaction with the highly efficient chain-transfer agent CBr_4, and these structures then function as centers of *cationic* chain growth (with Br as the counterion).

The photoinitiation leads first to radical-cations, whose ionic function is probably already capable of growing, while the free-radical function is again converted into a cationic 1-bromo-1-carbazylalkyl derivative by chain transfer with CBr_4.

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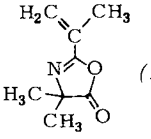
Inhomogeneous Polymer Networks through Incompatibility

By *Gerhard Markert* (lecturer) and *Horst Pennewiss*[*]

Copolymers of 4,4-dimethyl-2-isopropenyl-5-oxazolone *(1)*[1] with acrylic or methacrylic esters are crosslinked with diamines and investigated by torsional vibration experiments.



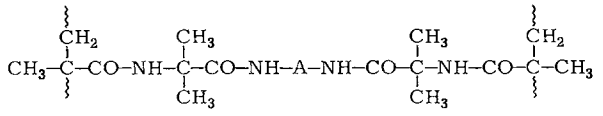
(1)

With increasing content of *(1)* (5 to 30 mole-%), increasing mechanical inhomogeneity is observed. There are two possible reasons for this:

a) a nonuniform distribution of the oxazolone groups,

b) a difference in the degree of intramolecular crosslinking.

In connection with the question of chemical inhomogeneity, the mechanical measurements are compared with calculations for the copolymerization. By variation of the



A = $(CH_2)_6$, $(CH_2)_{20}$, $(CH_2{-}\underset{CH_3}{CH}{-}O)_{\bar{n}-1}{-}CH_2{-}\underset{CH_3}{CH}$ with $\bar{n}$ = 4, 8, 16

crosslink length A, it is possible to influence the degree of intramolecular crosslinking, as can be seen from the determination of the conversion at the gel point.

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[1] *K. Hübner, F. Kollinsky, G. Markert*, and *H. Pennewiss*, Angew. Makromol. Chem. *11*, 109 (1970).

Polymerization and Copolymerization of 1,2-Dimethoxyethylene

By *Norbert Vollkommer*[*]

1,2-Dimethoxyethylene is prepared from trimethoxyethane by elimination of methanol in the gas phase in a fixed-bed catalyst.

Whereas no polymer is obtained with free-radical and anionic initiators, the polymerization can be initiated with

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cationic initiators. Organometallic compounds containing halogen and syncatalytic initiator systems are used in addition to Friedel-Crafts catalysts, perchlorates, and oxonium salts. Organoaluminum compounds containing chlorine, such as diethylaluminum chloride and ethylaluminum dichloride, have proved to be the most favorable group of cationic initiators.

The polymerization of dimethoxyethylene with this last group of initiators can be carried out particularly advantageously in the region around -50 °C with liquefied low-boiling aliphatic hydrocarbons as the suspension medium. The effects of the initiator concentration, the polymerization temperature, and the content of suspension medium on the polymerization conversion and molecular weight are investigated. Polydimethoxyethylenes having molecular weights ($\bar{M}_w$) of around 290000 can be obtained in almost quantitative conversions.

The principal properties of polydimethoxyethylene are reported, particularly the behavior in aqueous solution in the presence of electrolytes or water-soluble polymers, the absorption of water from the atmosphere at various atmospheric humidities, and a number of physical and mechanical properties.

Copolymerization experiments with monomers that polymerize with ring cleavage, such as six-membered ring carbonates and four-membered and seven-membered ring lactones, were also carried out.

Analysis of the Tacticity of Polymers by ^{19}F-NMR Spectroscopy

By *W. Regel* (lecturer), *L. Westfelt*, and *H.-J. Cantow*[*]

The ^{1}H- and ^{19}F-NMR spectra of monomeric *p*-fluoro-α-methylstyrene were discussed. The measured spectrum of the type AA'BB'X (X = ^{19}F) is in complete agreement with the calculated spectrum.

In cationically synthesized—predominantly syndiotactic—polymers, splitting of the α-proton signals at 220 MHz, and of the fluorine signals at 94.1 Hz, takes place according to the tacticities; the degree of splitting was found to be greater in the ^{19}F-NMR spectrum. The proportions of syndio- (83%) and of hetero-tactic triads (17%) calculated from the ^{19}F resonance are in agreement with those determined from the resonances of the α-methyl protons.

A heteronuclear decoupling technique (protons) especially developed for the Varian HA-100 spectrometer (100 MHz) led, as expected, to a single peak for the fluorine in monomers and to a splitting into pentads in the case of the polymers.

It could thus be shown that ^{19}F-NMR spectroscopy makes very good resolution of the *p*-fluorine nucleus possible in a short measuring time, even when the fluorine nucleus is far removed from the skeletal chain.

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Model Calculations for the Hydrolytic Polymerization of Caprolactam

By *Ferdinand Hafner*, *J.-C. Heilig*, and *Paul Wittmer* (lecturer)[*]

Caprolactam can be polymerized in various ways; the most important reaction from the industrial point of view is polycondensation or hydrolytic polymerization. Three equilibrium reactions occur together in this process (hydrolytic ring cleavage, polycondensation, and monomer addition). Amide groups also undergo transamidation.

We use kinetic equations for the formal description of the complete reaction. The constants required for numerical calculation were taken from the literature. One constant was changed from the literature value to obtain better agreement between the calculated values and the experimental results. Regulation by amine or carbonyl groups is taken into account.

The kinetic equations can be used together with formal patterns for reactors, *e.g.* residence-time spectra, for the mathematical simulation of the course of polymerization in given feed mixtures and reactors. This is a great help in the planning and optimization of reactors.

The equations are also suitable for the calculation of the rate of remonomerization on fusion of the delactamized polymer.

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The Initial Stage of the Oxidative Degradation of Native Cellulose by Molecular Oxygen

By *G. V. Schulz* (lecturer), *S. Jovanović*, and *A. Palma*[*]

Native Cellulose: Cotton bolls grown in a greenhouse are harvested immediately before or after they open, extracted with organic solvent, and boiled with 2% sodium hydroxide solution containing added Na dithionite. Result: A material that is completely soluble in cuprammonium solution or, after nitration, in acetone, contains no gel particles according to light scattering (LS) measurements, and consists to an extent of about 90% of molecules having a uniform degree of polymerization of 14000.

Degradation: 1. Treatment with 20% NaOH in the strict absence of oxygen at 20 °C. 2. The resulting alkali metal cellulose is exposed to molecular oxygen, and the decrease in the molecular weight (M_w) is followed by LS and [η] measurements. The molecular weight distributions of the nitrates were determined continuously during these treatments.

Result: The treatment with alkali alone leads to a considerable decrease in viscosity, whereas LS measurements show that M_w remains constant, the radius of gyration decreases, and the second osmotic virial coefficient A_2 increases. Other physical properties (density, refractive index) also change. Fractionation experiments show that these property changes occur practically uniformly in all the molecules. They may be regarded phenomenologically as a sort of molecular shrinkage process. The same effect is observ-

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ed in the cuprammonium solutions of the cellulose as well in the acetone solutions of the nitrate. It thus has considerable chemical resistance. The nitrates of the original cellulose and of the shrunk cellulose have equal nitrogen contents.

Interpretation: We assume that this shrinkage is due to intramolecular chemical crosslinking of the cellulose chains during the alkali treatment. More or less large rings are introduced into the dissolved molecule in this way, and these reduce the radius of gyration in solution. This interpretation is supported by the fact that oxidative cleavage of glucoside linkages in the alkali-treated material first leads to an increase in the intrinsic viscosity, while the molecular weight found by LS measurements remains unchanged; this means that after prolonged treatment with alkali, nearly all the glucose units are situated in the rings, whose cleavage increases the radius of gyration without reducing the molecule. The purely intramolecular nature of the crosslinking is shown by the fact that the molecular weight distribution of the alkali-treated material has no detectable component with a degree of polymerization higher than 14000.

Conclusion: The cellulose molecules must be folded in the elementary fibrils.

Growth of Crystals of Polyoxymethylene during Equilibrium Polymerization of Trioxane

By *Rosa Mateva* and *G. Wegner* (lecturer)[*]

It has long been suggested that polymerization and crystallization are coupled in the cationic polymerization of trioxane. We have therefore investigated the growth of the hexagonal platelets of POM formed immediately after addition of the catalyst (BF_3Et_2O) with the aid of electron-microscope methods. The results can be correlated with measurements of the conversion, the molecular weight, the specific gravity, the melting behavior, and the thermal stability of the polymers obtained.

At the end of the nucleation period, lamellar single crystals about 80—150 Å thick and about 1 µm in diameter are present. The chains are folded in the usual manner in these lamellas. It is surprising to note that these crystals increase both in thickness and in diameter with increasing conversion. This growth continues even after the limiting conversion imposed by the prevailing ceiling equilibrium has been reached. The driving force of this reaction is the minimization of the free surface energy of the microscopic crystals present, which are in equilibrium with one another *via* the polymerization-depolymerization equilibrium in the presence of the catalyst; thus smaller crystals redissolve, while larger crystals continue to grow.

The lateral growth of the crystals takes place by the normal polymerization reaction. The increase in thickness, on the other hand, results from the insertion of monomer into the chain folds of the surfaces of the lamellas. This reaction proceeds uniformly from the crystal-chemical point of view, with formation of growth spirals. The thickness of the crystals increases to an average of about 3000 Å. These crystals formed in thermodynamic equilibrium have the character of extended chain-crystals.

The results described a) can be generalized for numerous ring opening polymerizations in which crystalline polymer is formed, and b) are important to the theory of copolymerization in such systems. [VB 326 IE]

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Structural Chemistry of Mercury

By *Drago Grdenić*[*]

Until recently[1] the only known mercury compound with a purely ionic structure was mercury(II) fluoride which has the cubic CaF_2-type structure. At present, ternary fluorides with the perovskite-type structure, and fluorometalates with the VF_3-type or $LiSbF_6$-type structure are known[2] in which mercury has octahedral coordination. In all other structures, even those involving oxygen, *e.g.*, the oxide, oxide halides, hydroxide halides, and salts of oxoacids, mercury is covalently bonded within an irregular coordination polyhedron. This is also true for the structure of mercury(II) hydroxide fluoride[3] containing chain-like cations

—(OH)—Hg—(OH)—Hg—

with an Hg—O bond length of 2.06 Å.

The free molecules or complexes of the mercury compounds contain either two collinear, three coplanar, or four tetrahedral bonds involving mercury. These bonds, defining the characteristic[4] coordination about mercury, are approximately equal to the sum of the covalent radii if 1.30, 1.37, or 1.48 Å is taken for the respective covalent radius of mercury. No structure containing an individual complex with the mercury atom in octahedral coordination has been reported up to now. The characteristic linear or trigonal coordination about mercury is completed in the crystal structure to the effective[4] coordination with the coordination number four, five, or six accomplished in a "distorted" tetrahedron, trigonal bipyramid, or octahedron. The effective coordination about mercury includes all atoms whose distance from the mercury atom is less than the sum of the van der Waals radii, 1.50 Å being taken for the van der Waals radius of mercury.

The lengths of the characteristic bonds are affected less than the angles between them, particularly in the "tetrahedral" effective coordination. The collinear characteristic bonds persist in many crystal structures as the two shortest bonds, the additional bonds in the effective "octahedral" coordination being either equal or, usually, equal in pairs. The equatorial angles at mercury deviate from 90° but the centrosymmetrically distorted octahedron is quite common. The collinearity of the Hg—C bonds also persists in the crystal structure of the symmetric organomercury compounds and is only slightly influenced by the ligands introduced. The substituted atoms or groups in the organic part of the molecule may affect the collinearity of the Hg—C bonds as well as the coplanarity in the molecule of the aromatic derivative.

According to recent results[5] there is no correlation between the electronegativity of the ligands and the Hg—Hg bond length in the mercury(I) compounds. Hg—Hg distances from 2.495 to 2.540 Å were found in thirteen crystal structures with an average of 2.508 Å. This is less than the sum of the covalent radius of 1.30 Å for collinear bonds in mercury(II) compounds, probably because of the d_π-p_π contribution to the Hg—Hg bond. The coordination

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about mercury in mercury(I) compounds does not show any regularity. All known structures of the mercury(I) salt hydrates contain the oxonium group

$H_2O—Hg—Hg—OH_2$

with an Hg—O bond length between 2.14 and 2.20 Å. Chelate ligands or the anions of oxoacids are not symmetrically coordinated to the Hg—Hg ion. In mercury(I) arsenate[6] the smallest Hg—O distances lie between 2.16 and 2.23 Å, while in mercury(I) trifluoroacetate[7] this distance is 2.14 Å. It is interesting that no organomercury compound with Hg—Hg—C bonding has yet been described.

Lecture at Giessen (Germany), December 5, 1972 [VB 367 IE]
German version: Angew. Chem. 85, 418 (1973)

[1] *D. Grdenić* in *K. H. Wedepohl:* Handbook of Geochemistry, Vol. II/1. Springer-Verlag, Berlin 1969, p. 80-A-1.

[2] *R. Hoppe et al.*, Z. Anorg. Allg. Chem. *368*, 271 (1969); *369*, 212 (1969); *376*, 261 (1970); *392*, 1 (1972).

[3] *D. Grdenić* and *M. Sikirica*, Inorg. Chem., in press.

[4] *D. Grdenić*, Quart. Rev. Chem. Soc. *19*, 303 (1965).

[5] *E. Dorm*, Chem. Commun. *1971*, 466.

[6] *B. Kamenar* and *B. Kaitner*, personal communication.

[7] *M. Sikirica* and *D. Grdenić*, to be published.

ABSTRACTS

Reviews

Abstracts of selected progress reports and review articles

Ionic solvation in nonaqueous and mixed solvents is the title of a review by *J. I. Padova*. The author deals with: Thermodynamics of solvation and the determination of corresponding parameters (heat of reaction, free energy, and entropy); theory of solvation; solvation numbers; solvation in mixed aqueous-organic solvents; and transport processes (viscosity, electrical conduction, Stokes' law Walden's rule, association processes). [Ionic Solvation in Nonaqueous and Mixed Solvents. Mod. Aspects Electrochem. *7*, 1—82 (1972); 431 references]

[Rd 562 IE—G]

Recent developments in the catalysis of hydroformylation feature in a review authored by *F. E. Paulik*. After carbonylcobalt had long been considered the catalyst of choice and progress been restricted essentially to variations in process parameters, the chemistry of organic transition metal complexes afforded new scope for catalyst modifications which have led to reduced reaction temperatures and pressures and greater selectivity and stability of catalysis. Metal complexes with organophosphanes as ligands have proved to be particularly suitable and the publication therefore concentrates mainly on these catalysts. [Recent Developments in Hydroformylation Catalysis. Catal Rev. *6*, 49—84 (1972); 62 references]

[Rd 565 IE—G]

Catalyst studies with the aid of a temperature-programmed desorption technique are summarized by *R. J. Cvetanovi* and *Y. Amenomiya*. In this technique, which was first described by the authors in 1963, gas adsorbed on a catalyst is desorbed in a stream of inert carrier gas by programmed heating of the catalyst. The method has the advantage that no ultra-high vacuum is required and the conditions more closely resemble those encountered in practice. The literature is covered up to 1971 and a detailed account is given of Al_2O_3, SiO_2/Al_2O_3, carbon, metal oxides, and metals as catalyst materials. [A Temperature Programmed Desorption Technique for Investigation of Practical Catalysis. Catal. Rev. *6*, 21—48 (1972); 47 references]

[Rd 567 IE—G]

NMR in ferromagnets and antiferromagnets is the subject of a survey by *M. P. Petrov* and *E. A. Turov*. NMR is one of the most informative methods available for the study of the spatial distribution of local magnetic fields and spin density, of interactions between electrons and nuclei, and of the temperature dependence of magnetic moments. The pronounced changes in the NMR frequency and relaxation time with the temperature, *e.g.* in MnF_2, permits precise measurement of temperature between 10 and 40 K with an accuracy of 10^{-4} K. [Nuclear Magnetic Resonance in Ferromagnets and Antiferromagnets. Appl. Spectrosc. Rev. *5*, 265—330 (1972); 119 references]

[Rd 572 IE—G]

Concepts of reaction dynamics are discussed in a review by *J. C. Polanyi*. Starting from the concept of (attracting and repelling) energy surfaces the author discusses the individual collision processes in exothermic, endothermic, and thermoneutral reactions as well as reactions involving high collision energies. Energy distribution in reaction products is also dealt with. [Some Concepts in Reaction Dynamics. Accounts Chem. Res. *5*, 161—168 (1972); 43 references]

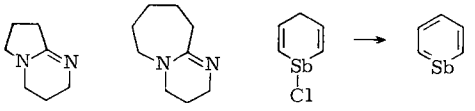
[Rd 596 IE—L]

The determination of the conformation of cyclic polypeptides in solution is discussed by *F. A. Bovey*, *A. I. Brewster*, *D. J. Patel*, *A. E. Tonelli*, and *D. A. Torchia*. It is shown that not only NMR but also IR, CD, and ORD data can be used in conjunction with energy calculations to give a self-consistent structure (or structures). Especially conclusive are the coupling constants of the α-CH- and NH-protons of the peptide skeleton.—Synthetic cyclohexapeptides as well as the decapeptide antamanide, the nonapeptide cyclolinopeptide A, and phalloidine, whose confor-

mations are illustrated as space filling models, are used as examples. [Determination of the Solution Conformation of Cyclic Polypeptides. Accounts Chem. Res. 5, 193—200 (1972); 69 references]

[Rd 599 IE—L]

The use of bicyclic amidines such as *(1)* and *(2)* in organic syntheses is reviewed by *H. Oediger, F. Möller,* and *K. Eiter. (1)* and *(2)* rapidly eliminate, *inter alia,* hydrogen



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

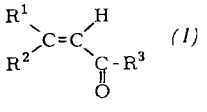
halides under mild conditions; thus it proves possible to obtain the extremely unstable compound stibabenzene *(3)*. Moreover, sulfonic acids are eliminated from their esters and HNO from nitroso compounds. *(1)* and *(2)* also possess catalytic properties. [Bicyclic Amidines as Reagents in Organic Syntheses. Synthesis *1972*, 591—598; 49 references]

[Rd 602 IE—M]

Patents

Abstracts of selected "Deutsche Offenlegungsschriften" (DOS), *i. e.* provisionally published specifications as filed with the German Patent Office

Resin compositions or objects made from them that are decomposed and degraded by the action of light and whose destruction does not present the usual problems of environmental pollution consist of 1) 50—100 wt.% of a copolymer of a) 95—99.9 wt.% of styrene and/or methyl methacrylate, b) 5.0—0.1 wt.% of a diene monomer such as butadiene or isoprene, and c) up to 4.9 wt.% of an unsaturated ketone having the general formula *(1)*, such as methyl vinyl

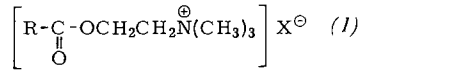


(1)

ketone, phenyl vinyl ketone, phenyl propenyl ketone, and/or benzylideneacetophenone, and 2) up to 50 wt.% of a thermoplastic resin that is different from *(1)*, *e.g.* polystyrene, PVC, polyethylene, *etc.* [DOS 2165157; Sekisui Kagaku Kogyo K. K., Osaka]

[PR 60 IE—O]

Antistatic agents for the treatment of high polymers that retain their antistatic activity irrespective of the mode of application and exhibit good compatibility with the high polymer are choline ester salts having the general formula *(1)*, *e.g. N*-(hexanoyloxyethyl)- or *N*-(octanoyloxyethyl)-trimethylammonium chloride. The compounds *(1)* are



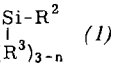
(1)

R = straight-chain alkyl group C_5-C_{17}
$X^{\ominus}$ = singly charged anion, preferably $Cl^{\ominus}$ or $NO_3^{\ominus}$

advantageously added together with 3—20% (based on the total quantity of antistatic) of choline chloride to the polymers, particularly polyolefins, PVC, polystyrene, or their copolymer mixtures. [DOS 2157290; Unilever N. V., Rotterdam]

[PR 61 IE—O]

Antithrombogenic plastic components consisting of *e.g.* polyethylene, polypropylene, or polystyrene, PVC, polyvinyl acetate, or polyacrylonitrile are obtained by bonding a heparin layer to an aminosilane coupler having the general formula *(1)*. R^1 denotes halogen or alkoxy, R^2 is amino-



(1)

alkyl, R^3 is alkyl, and $n = 1$—3. The surface of the resin is first impregnated with the aminosilane *(1)* and a swelling agent until it is swollen and the aminosilane is bonded to the resin. The aminosilane *(1)* is protonated by sufficiently long immersion of the resin in an aqueous acidic salt solution. The plastic component is then immersed in an aqueous acidic solution of a heparin salt, whereupon the heparin is bonded to the aminosilane coupler *(1)*. The plastics treated in this way are used in medicine as materials for artificial organs, since clotting or hemolysis on contact with blood or serum is suppressed. [DOS 2154542; Corning Glass Works, Corning]

[PR 84 IE—E]

A hydrogen transfer reaction for the preparation of unsaturated compounds, preferably having a diene structure, starts with unsaturated compounds A, which serve as hydrogen donors, and organic hydrogen acceptors B; catalysts based on complexes of Group VIII metals in which the metals are present in a low valence state are used. The reactants A and B may be the same or different, and must contain at least one ethylenically unsaturated bond. The process can be applied both to aliphatic and to cycloaliphatic unsaturated compounds, as well as to unsaturated compounds having functional groups, such as nitrile, ester, or ether groups. Conjugated dienes with a well-defined steric configuration are obtained. — In one example, hexene, which serves both as A and B, is allowed to react in the presence of $IrH_3[P(C_6H_5)_3]_2$ to form hexane and *trans,trans*-2,4-hexadiene. The reaction is carried out in an inert solvent, preferably in an inert atmosphere and with the addition of small quantities of hydrogen, above normal temperature and at or above normal pressure. [DOS 2149934; Snam Progetti S.p.A., Milan]

[PR 76 IE—U]

Oxonium Ions in Organic Chemistry. By *H. Perst*. Verlag Chemie GmbH, Weinheim/Bergstr. and Academic Press, New York—London 1971. 1st ed., ix, 202 pp., 6 figs., 12 tables, cloth DM 55.—.

The importance of oxonium compounds in organic chemistry is due partly to their great preparative value, particularly in alkylations, and partly to the fact that they are reactive intermediates in many organic reactions.

In seven chapters, this book summarizes the present knowledge of oxonium ions in organic chemistry, which has not yet reached unmanageable proportions. After a brief introduction to historical development (4 pp.), classification and nomenclature of oxonium ions are discussed (6 pp.), followed by a section on their stability (11 pp.). The fourth chapter deals with formation and methods of preparation (35 pp.), Chapter 5 with the reaction behavior of oxonium salts (42 pp.). Reactions which proceed *via* oxonium ions, or where oxonium ions are supposed to be reactive intermediates, are summarized in Chapter 6 (27 pp.). In the last section, the application of oxonium salts in synthetic work is described (39 pp.). An appendix concerning the structure of oxonium ions refers mainly to protonation products of carbonyl compounds investigated in recent years by NMR spectroscopy.

In the discussion of unsaturated oxonium ions, differentiation from carbonium ions presents a fundamental difficulty since, due to electronegativity differences, the positive charge will be localized predominantly at carbon atoms. It would, therefore, have been better to omit the rather lengthy discussion of the carbo-cation problem (see *e.g.* pp. 13 *et seq.*, 63 *et seq.*, or 78 *et seq.*) in favor of "true" oxonium ions. In the reviewer's opinion, this objection also applies to the much too detailed presentation of pyrylium salts which have been given much more space than trialkyloxonium salts, both in the chapter on methods of preparation and that on synthetic application.

The presentation of a number of tables must be criticized. To recognize all details in Table 9, for example, one needs good light and above-average vision or the aid of a magnifying glass. The continuous numbering of formulas does not offer much of an advantage since most structural formulas are reproduced several times in any case, and the literature references are numbered chapter by chapter.

Apart from these minor shortcomings, however, the book provides a very good synopsis of an important class of compounds, and thus is a welcome addition to the review literature.

Franz Effenberger [NB 151 IE]

Recent Books

The following books have been received by the editor. Detailed reviews will not be published in all cases because of the limited space available under this heading in the journal.

Bindung, Struktur und Reaktionsmechanismen in der organischen Chemie (Bonding, Structure, and Reaction Mechanisms in Organic Chemistry). By *I. Ernest*, Springer Verlag, Wien New York, 1972, x, 389 pp., bound DM 98.—.

Contents: Structure of organic compounds; general characteristics and classification of organic reactions; polar reaction; free radical reactions; multicenter reactions involving cyclic electron shifts.

Radiochemistry, Vol. 1. By *G. W. A. Newton, G. R. Gilmore*, and *J. D. Hemingway*. The Chemical Society, London 1972. vii, 131 pp., bound £4.50.—A volume in the series "Specialist Periodical Reports".

Organometallic Chemistry, Vol. 1. By *E. W. Abel* and *F. G. A. Stone*. The Chemical Society, London 1972. xvi, 521 pp., bound £9.00.—A volume in the series "Specialist Periodical Reports".

Kunststoffe von A–Z (Plastics from A—Z). By *H. Blau*. Bertelsmann Lexikon-Verlag, Gütersloh, Berlin, München, Wien 1973. 178 pp., linen DM 9.80.

Contents: A lexical guide.

Guide for Safety in the Chemical Laboratory. Edited by the Manufacturing Chemists Association. 2nd Edit., Van Nostrand Reinhold, London, New York, Cincinnati, Toronto, Melbourne 1973 xvi, 505 pp., bound £ 8.75.

Amino Acids, Peptides and Proteins, Vol. 4. By *G. T. Young*. The Chemical Society, London 1973. xvi, 498 pp., bound £ 9.00.—A volume in the series "Specialist Periodical Reports".

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Light Guide Systems for the Ultraviolet Region of the Spectrum

By Helmut Dislich and Alfred Jacobsen[*]

Whereas diverse and highly refined fiber optics have long been in technical use for the conduction of visible light, traditional but expensive silica glass lenses and prisms have had to be utilized until quite recently for the transmission of ultraviolet light. The reason for this was the lack of suitable materials. UV light cannot be transported to any technically useful extent either with pure glass-glass (core and sheath materials) light guides or with plastic-plastic light guides. UV light guides for wavelengths down to 200 nm can be produced by combination of a silica glass as the core material with a tetrafluoroethylene-hexafluoropropylene copolymer or methylpolysiloxane as the sheath material. Fiber optics of this type constitute a new aid for medical technology, medicine, and many technical and scientific fields, whose range of applications cannot yet be fully envisaged.

1. The Principle of Light Conduction

If a rod or a fiber made of transparent material having a high refractive index n_1 is coated with a transparent sheath of a material having a lower refractive index n_2, light falling on the end surface is conducted through the rod or fiber as a result of total reflection. The light is reflected without loss at the interface between these media (whereas loss occurs on reflection at a mirror surface), and is transmitted through the system in a zigzag path until it emerges at the other end. Important characteristics of such systems are:

1. the light transmittance
2. the aperture angle.

Both should be as large as possible. To achieve this, the core material in particular should have excellent transmittance, and the sheath layer, which should also be transparent, should have an excellent optical contact with the core. This means that the sheath must be in smooth and uniform contact at all points to allow loss-free total reflection. The difference between the refractive indices $n_1 - n_2$ should be as large as possible, since this determines the aperture angle $2\alpha_0$ at which light can be conducted (see Fig. 1) in accordance with

$$n_0 \sin \alpha_0 = \sqrt{n_1^2 - n_2^2}$$

(n_0 is the refractive index of the surrounding medium).

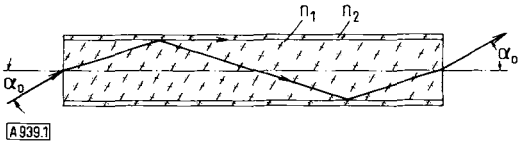

Fig. 1. Principle of light conduction.

1.1. Known Systems

The simplest case of light conduction is when light is transmitted along a straight or only slightly curved (radius

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of curvature >20 diameters) path through an unsheathed rod of glass or plastic. The surrounding air then acts as the low-refractivity sheath. Systems of this type have serious disadvantages since the optically effective sheath surface is exposed, and scratches and dust deposits lead to light scattering and hence to losses. The light guides used in practice are therefore predominantly of the sheathed variety.

The sheathed systems correspond to Figure 1, and those consisting of massive rigid rods require no further description. However, flexible light guides consisting of bundles of fibers have become much better known, if only because of the fact that they can be used to "guide light round corners", and in the case of "coherent bundles of fibers" one can actually see round corners, a possibility that fascinates even the optical layman. The light in this case is led through optically isolated flexible fibers as illustrated in Figure 1. A large number of these fibers are combined into a bundle, the fibers being cemented together at the ends and polished. The bundles are enclosed in a protective metal or PVC tube, and can be widely used in medicine (endoscopy) and in industry. If the arrangement of the fibers in relation to one another at the point where the light enters corresponds to that at the point where the light emerges, transmission of images is possible. If the fibers are unordered, they can be used only for the transmission of light.

Finally, mention should be made of fiber rods; these also consist of a large number of optically isolated fibers, which are fused together over their entire length and are therefore rigid. These are coherent, *i.e.* capable of transmitting images, and can be subsequently bent round relatively sharp corners.

Arising from these basic types there are a large number of interesting variations, which greatly extend the existing possibilities in optics. However, it is not the aim of this report to present a comprehensive description of the current position in this respect. Such an account has appeared elsewhere[1].

2. Materials

To lead up to the subject proper, let us first consider the question of the materials that can be used. As was mentioned above, the decisive factor is the light transmittance. The traditional material of optics is glass. The entire development of fiber optics in the Jenaer Glaswerk Schott & Gen. was carried out with high-quality optical glasses, so that both the cores and the sheaths of the commercially available products[2] consist of glass.

The possibility of using pure plastics systems has been under discussion for a long time. *Kapany*[3] showed that the fiber-forming polymers in the drawn state have disadvantages in comparison with glass fibers because of the anisotropy resulting from their partial crystallinity. He also noted disadvantages with regard to surface quality. However, the flexible systems developed by Du Pont[4,5] are produced from plastics. These consist of a polymethyl methacrylate core and a low-refractivity sheath of partly fluorinated plastics.

We were interested in plastics only as sheath materials, as we wished to take advantage of the outstanding properties of glass as a core material, in particular its good optical transmittance, surface accuracy, and polishing qualities of the end faces where the light enters and emerges.

2.1. The Core Material of the UV Guides

All the possibilities discussed so far are concerned with the conduction of visible light, in some cases extending into the near infrared region. Ultraviolet light with shorter wavelengths could not be conducted, since the transmittance of the core materials was insufficient. For light with wavelengths of down to 200 nm, there is no choice as far as core materials are concerned; practically the only possibility is high-purity silica glass, which must be of outstanding optical quality (in particular free from bubbles), and which can be drawn to fibers. We used Suprasil® (manufacturer: Heraeus-Schott, Quarzschmelze GmbH). For light having a wavelength of 365 nm, it is occasionally possible, within limits, to use special UV-transparent glasses if the optical path length is not excessive. However, this possibility is mentioned only in passing, as it is of no fundamental importance.

2.2. The Sheath Material of UV Fiber Optics

Flint glass has the following refractive indices at various wavelengths: $n_{546}=1.460$; $n_{365}=1.475$; $n_{155}=1.506$.

An optically isolating material for silica glass must therefore consist of a material that has a sufficiently low refractive index at all wavelengths and that is transparent to light of the wavelength in question.

One's first thought is naturally of the wide range of optical glasses, which is shown in Figure 2 in the form of the usual $n_d-\nu_d$ diagram. n_d is the refractive index for the d line (587.6 nm), and ν_d is the Abbé number, a measure of the dispersion.

Though the optical catalog of the Jenaer Glaswerk Schott & Gen. lists several hundred types of optical glasses, it is immediately clear that these do not include one with a sufficiently low refractive index to make it suitable for use as a sheath material. Here we reach a limit to the current optical possibilities of glasses. The present limit of the glass range in the direction of low refractive indices is shown by a broken line in Figure 2. The continuous lines are the limits of the individual glass types. The dot-dash line surrounds the region of the transparent plastics. In the direction of higher refractive indices, the glass region extends far beyond the top of the diagram.

Since glasses offer no further help with regard to a suitable sheath material, the next step is to consider other inorganic, UV-transparent materials with extremely low refractive indices. One such material is magnesium fluoride, which is commonly used as a transparent coating deposited from the vapor phase, *e.g.* as an antireflective coating on optical lenses.

While the properties of the material are promising, the technical difficulties of the vapor deposition of coatings

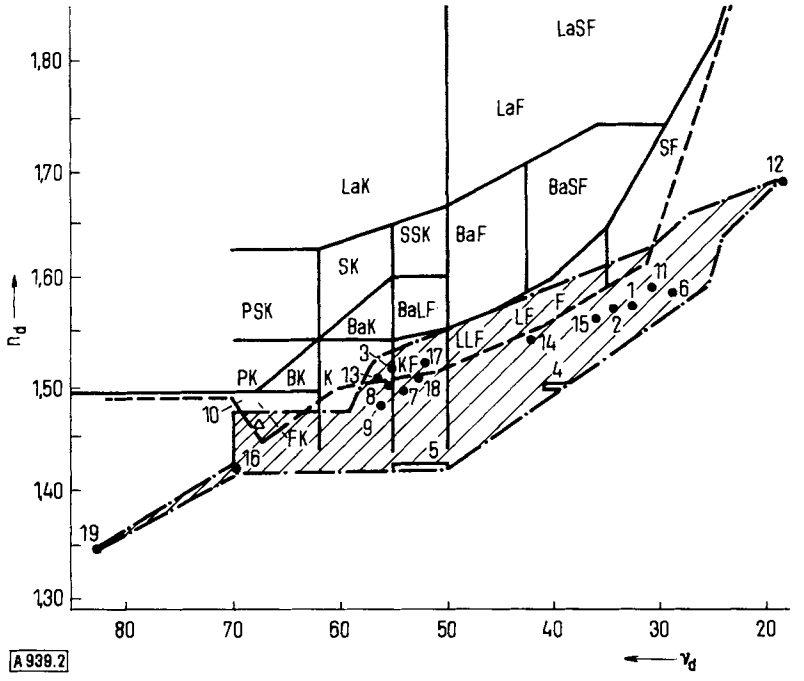


Fig. 2. Glass region and plastic region in the $n_d - \nu_d$ diagram. $\nu_d = (n_d - 1)/(n_F - n_C)$ (Abbé number). n_F, n_C: refractive indices for the F and C lines. ---: present limit of the glass region, -·-·-: present limit of the region of transparent plastics having known $n_d - \nu_d$ values. Δ: silica glass; •: plastics 1—19. 1, styrene-acrylonitrile copolymer; 2, poly-*o*-diallyl phthalate; 3, polymethyl α-chloroacrylate; 4, methylphenylpolysiloxane; 5, methylpolysiloxane; 6, poly-α,α-dimethyl *p*-(*p*-hydroxyphenylmethyl)phenyl hydrogen carbonate; 7, polymethyl methacrylate; 8, polydiethylene glycol diallyl carbonate; 9, cellulose acetate; 10, cellulose propionate; 11, polystyrene; 12, poly-*N*-vinylcarbazole; 13, polycyclohexyl methacrylate; 14, polyvinyl chloride; 15, epoxy resin (Araldite CY 206); 16, poly-2,2,2-trifluoroisopropyl methacrylate; 17, methyl methacrylate-α-methylstyrene copolymer; 18, methyl methacrylate-acrylonitrile copolymer; 19, tetrafluoroethylene-hexafluoropropylene copolymer (Teflon FEP).

several μm thick on fibers impose such severe limits that technically useful products are unobtainable[6].

2.3. Optical Properties of Plastics

Another alternative to the classical materials of optical glasses is offered by the transparent plastics, whose region is indicated by the shaded area in the $n_d - \nu_d$ diagram (Fig. 2). It is interesting to note that the region of the transparent plastics extends considerably beyond that of the glasses, and coincides only in part with the latter[7].

A general comparison of the positions in the $n_d - \nu_d$ diagram (optical positions) with the chemical structures of the polymers reveals simple principles, which have been fundamentally known for a long time[8], and which are simply confirmed or expanded by newly developed plastics.

Highly aromatic plastics such as polystyrene, polyaryl carbonates, or even poly-*N*-vinylcarbazole have high refractive indices and low Abbé numbers; fluorinated and particularly perfluorinated polymers are characterized by low refractive indices and high Abbé numbers.

With the aid of the Lorentz-Lorenz equation

$$R_M = \frac{n^2 - 1}{n^2 + 2} \frac{M}{d}$$

R_M = molar refraction, M = molecular weight, d = density, n = refractive index

it is possible to estimate (and even to calculate fairly satisfactorily with the aid of atomic, group, and bond refractions if the density is known) the hypothetical limits for the optical position of the plastics[8]. If hypothetical polymers are speculatively included in this calculation, one arrives at the result that as far as one can see at present, there will presumably be no polymers with refractive indices appreciably above $n_d = 1.73$ or below $n_d = 1.33$, and that the center of the glass region cannot be reached with plastics.

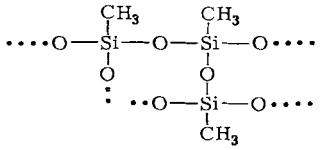
It may be noted in passing that this places limits on the competition that is sometimes referred to between optical glasses and plastics. The competition arises in the region of overlap between glasses and plastics. In general, however, a more interesting area in optics is that of glass-plastic combinations, particularly here in the case of UV light guides.

Plastics have recently become available whose chemical structure, according to the relations discussed here, suggests that they should have optical properties such as are required of a sheath material for UV light guides. These materials are methylpolysiloxane and tetrafluoroethylene-hexafluoropropylene copolymer (points 5 and 19 respectively in Fig. 2).

2.4. Methylpolysiloxane

Where can we find a material for coating rods or fibers of silica glass which has a refractive index lower than that of silica glass and a good UV transparency? Such properties are embodied in a methylpolysiloxane that became known in an optical quality in the middle 1960's[9],

in which the Si—O skeleton of silica glass carries one methyl group per silicon atom, the lowest possible degree of substitution.



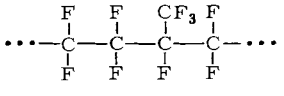
It is obtainable in principle by hydrolysis and polycondensation of a methyltrialkoxysilane $CH_3—Si(OR)_3$[9], and is trifunctionally crosslinked in the cured state. The optically perfectly clear material, while very transparent to UV light, has sufficiently low refractive indices as a result of the incorporation of CH_3 groups. The refractive index has fallen from 1.460 to 1.418 at 546 nm and from 1.475 to 1.453 at 365 nm.

A silica glass rod is immersed in a 50% solution of partly condensed methyltriethoxysilane in alcohol, withdrawn at a constant rate (in addition to other parameters, this mainly determines the coating thickness), and heated to a maximum of 135 °C. The silica glass rod is thus provided with a sheath of very good optical quality, and exhibits an aperture angle of $2\alpha_0 = 29°$ at 365 nm.

While some of the problems in the transport of UV light were solved with these rigid light guides[10, 11], flexible UV fiber optics still remained as the principal aim. A silica glass fiber can in principle be coated continuously, as required here. However, the curing times for the above polycondensation are too long for production, particularly when good optical quality is essential. Further investigations were therefore carried out with the object of finding a plastic with a still lower refractive index and a shorter setting time.

2.5. Tetrafluoroethylene-Hexafluoropropylene Copolymer

Point 19 in Figure 2 shows the extreme optical position of the material known by the trade name Teflon FEP®. With $n_{546} = 1.347$, $n_{365} = 1.356$, and $n_{255} = 1.376$, it has a lower refractive index than any other plastic known at present. Because of its branched structure as a copolymer



of tetrafluoroethylene and hexafluoropropylene, it does not exhibit the strong crystallization tendency of polytetrafluoroethylene, and so remains sufficiently transparent. Coatings of very fine particles can be applied from aqueous dispersions, and after removal of the water and the dispersing aids by heating, these particles can be fused to form a continuous, optically satisfactory film. This is again a property of the copolymer that it does not share with polytetrafluoroethylene.

We shall not go into details of the technically interesting as well as troublesome development of the continuous coating of a silica glass fiber 100 µm in diameter[12]. The first requirement was to draw a bubble-free, stria-free, and scratch-free fiber of uniform thickness continuously from silica glass. This fiber was passed through the aqueous dispersion of Teflon FEP and then through a long furnace. The processes of drying, evaporation of the dispersing aids, and fusion of the remaining Teflon FEP particles to form a continuous film required accurate adjustment of temperature gradient and of time, mainly because of the need to avoid thermal decomposition of the copolymer. Special care was necessary to lead the relatively fragile fiber over many guiding rollers without damaging its surface[*].

The essential point seems to be that the problem of the conduction of UV light by any desired route to any desired place has been solved[12] by combination of the outstanding UV transmittance of silica glass and its ability to be drawn into fibers with the good UV transmittance and the extremely low refractive index of a polyperfluoroalkane[13], and that this is the only solution found so far.

Figure 3 shows the spectral transmittance of flexible UV light guides in the form of a bundle of fibers.

3. Construction and Uses of UV Light Guides

The coated silica glass fibers have recently been used, mainly during the past year, for the development of many UV-conducting components, which have been included by the Industrial Research Council in the USA (Chicago) among the hundred most significant new technical developments of 1972. The product should be regarded primarily as a new tool for medical technology, medicine, physics, materials testing, photochemistry, and many other fields extending as far as genetics.

3.1. Properties

The system is optically transparent between 200 and 2200 nm; this range is interrupted only by an absorption band at 1400 nm and some weak harmonics of the OH absorptions. The optical transparency was measured with light entering the light guide at an aperture angle of 5°. The significant feature is the relatively high, uniform transmittance in the visible and near UV regions (Fig. 3). Light guides 1800 mm long reach values of more than 40% in the region between 280 and 1300 nm.

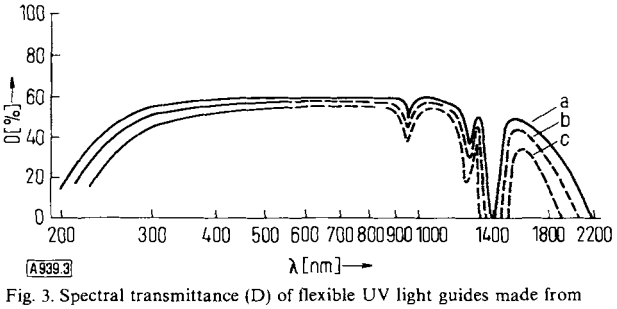


Fig. 3. Spectral transmittance (D) of flexible UV light guides made from silica glass coated with Teflon FEP. Length of light guide: a, 500 mm; b, 1000 mm; c, 1800 mm.

[*] Thanks are due in particular to Dr. *Buyken* for development to the production stage.

The second important property of the UV light guides is their aperture angle. The better the optical contact between the fiber core and the sheath, the smaller are the losses in the numerous total reflections.

Light rays substantially parallel to the optical axis accordingly suffer little loss. Light rays entering the fiber at angles close to the critical angle of incidence α_0 suffer losses that increase with the length of the fiber. Since the angle relationship between the incident light rays and the optical axis remains substantially unchanged, it is found in practice that the aperture angle varies with the length of the light guide. The results of measurements are shown in Figure 4.

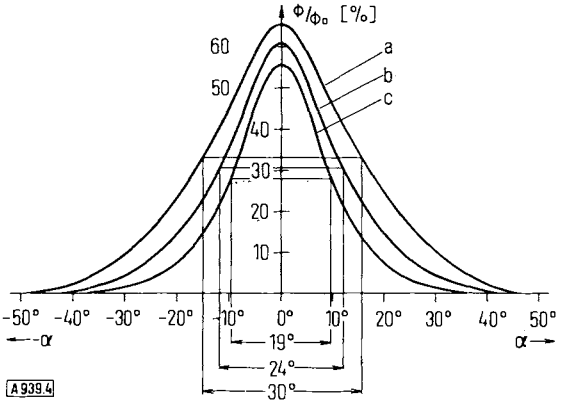


Fig. 4. Angular distribution of the emerging radiation characteristic at 546 nm for silica glass coated with Teflon FEP. Length of light guide: a, 500 mm; b, 1000 mm; c, 1800 mm. The values in the center between the arrows are 2α (50%).

Flexible UV light guides were illuminated uniformly from all directions at the entry end. The intensity distribution of the light emerging from the light guide as a function of the angle with respect to the optical axis shows different opening angles for different lengths if one considers the half widths of the bell-shaped curve. For glass-glass light guides, this value corresponds to the theoretically calculated aperture angle $2\alpha_0$, and is independent of the length of the light guide. This is an indication of the excellent optical contact between fused glasses. The junction between silica glass and the plastic used here is not so perfect, hence the dependence of the aperture angle on the length. One can theoretically expect $2\alpha_0 \approx 68°$; however, the measured aperture given in Fig. 4 is adequate for practical purposes.

Flexible UV light guides possess good stability to UV radiation. The optical transmittance was unchanged by continuous irradiation for a period of several thousand hours with light of wavelength 254 nm at a light density of 1 mW per 4 mm^2 cross section of bundle.

Much greater light intensities can be transmitted at long wavelengths, *e. g.* 320 nm, since solarization effects decrease exponentially with increasing wavelength. X-Radiation in a dose of about 10^5 r causes a decrease in transmittance only in the short-wave region, whereas no adverse effects are detectable in the visible region of the spectrum.

The heat stability of flexible UV light guides depends essentially on their protective tube and on the cement used to bond the fibers at the ends of the bundle. Whereas the light-guide fibers themselves can withstand continuous exposure to temperatures of 250 °C without loss of transmittance, the maximum temperatures to which the ends of the bundles may be exposed are 150—180 °C. On the other hand, no change in transmittance was observed on cooling to −200 °C.

Flexible UV light guides are resistant to water even at temperatures of up to 90 °C. A slight decrease in the optical transmittance occurs only in boiling water.

3.2. Applications of UV Fiber Optics

The uses of UV fiber optics are numerous, and their full extent cannot yet be seen. They considerably facilitate working with UV light. Commercially available UV light sources and the necessary mains equipment are relatively bulky at present. UV light guides enable UV light to be transported to places that are inaccessible to such bulky equipment, and UV light can therefore be used even inside complicated instruments (Fig. 5). Flexible light guides can

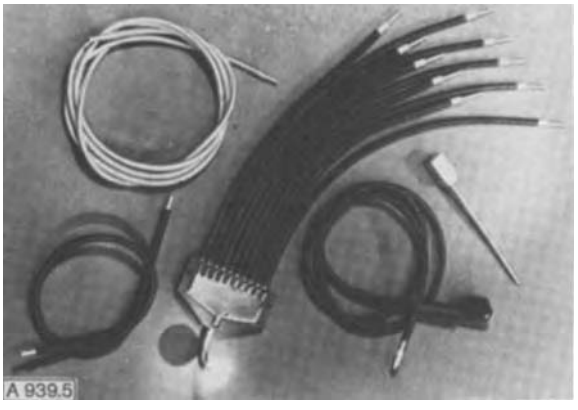


Fig. 5. Different types of light guide.

be led around many corners, like electrical wires, without loss of light. Where relative movement occurs between the UV light source and the receiver, UV light guides form a flexible connection. They serve as secondary light sources in explosion-proof areas or Faraday cages, leading the radiation into these structures easily and with low losses from UV light sources situated outside.

Flexible UV light guides help in many ways in the development of rational automatic analytical equipment for medicine, chemistry, and biochemistry. The transport path of the liquids to be investigated can be considerably shortened, since the light is brought to the point of investigation and the geometry of the UV light sources is of no importance, whereas it was formerly necessary to bring the liquid to the light source.

Wide fields of application arise in medicine, biochemistry, microscopy, and physiology through defined illumination or irradiation of objects with UV light. Certain drugs that accumulate in animal organs and tissues fluoresce on excitation with UV light (Fig. 6). The fluorescence

in the visible region of the spectrum can then be observed with other light guides or endoscopes or under the microscope.

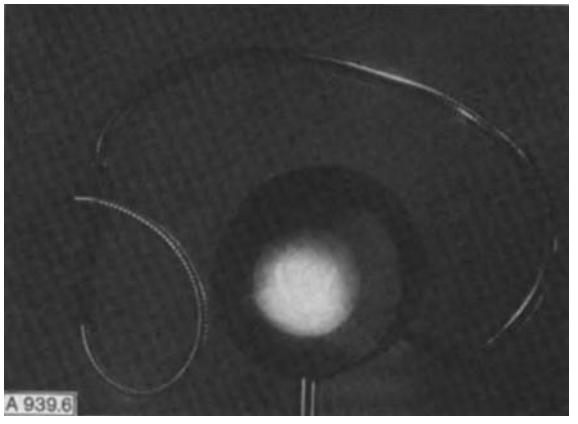


Fig. 6. A flexible light guide transmits UV light and excites fluorescence.

It should be noted that as early as 1964—1966[14] a specific absorption of certain antibiotics (tetracyclines) on carcinomas was observed, and (a decisive point here) the adsorbed antibiotics fluoresced on excitation with UV light. The fiber optics with limited UV transmittance that were available at that time were adequate for these experiments. Following this work, the recognition of cancer with the aid of UV fiber optics has at least become conceivable.

Possibilities for the use of UV light guides also occur in the field of plastics that polymerize and cure under the influence of UV light. Paints and adhesives can be treated very easily with flexible fiber optics. In dentistry, plastics have been developed for application to teeth as varnishes to provide protection lasting several years against caries. With UV light guides, the varnish can be irradiated and cured on the teeth in any dental practice.

Flexible UV light guides combined with light guides for the visible region of the spectrum as two-arm systems form ideal fluorescence light barriers. UV light is led to the point of investigation through one arm. The visible fluorescence light reaches a light-sensitive receiver through the other arm, which cannot transmit reflected UV stray light because of its spectral transmittance. Use is made of this possibility in labeling machines, the designation being printed in code with fluorescent ink and being read automatically. Two-arm UV light guides also give excellent results in automatic letter-sorting machines and stamp-cancelling machines. The actual UV light source is situated far from the reading point, and is accommodated where sufficient space is available in the machine. Numerous UV-conducting components are used in spectrographs, in which the light entering through a slit is led by a cross-section converter to a detector. The cross sections of the light guide can be matched to the geometry of the other optical and electro-optical components (cf. Fig. 6).

The possibilities of UV fiber optics have not yet been exhausted. The applications of UV light can still be greatly extended by means of this new tool for industry and science. Numerous light-guide systems with special dimensions and shapes are available for this purpose.

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Elemental Sulfur—A Challenge to Theory and Practice[**]

By Max Schmidt[*]

Surprisingly little is still known about many aspects of the system "elemental sulfur", in spite of its being one of the longest known and common "chemical substances" and today available cheaply and in great purity. This paper summarizes some of the newer investigations that have increased our understanding of this system.

1. Introduction

Four years ago the answers to a world-wide questionnaire that had been circulated to academic research Institutes were published[1]. Though certainly incomplete, these showed that at least 2250 scientists were then engaged in sulfur chemistry in no fewer than 275 laboratories.

Problems concerning sulfur chemistry arise in all branches of chemistry—from inorganic chemistry through biochemistry, organic chemistry, physical chemistry and industrial chemistry to purely theoretical chemistry and finally also in environmental pollution.

From the many known and still unknown sulfur compounds our School is at present interested particularly in those molecules in which at least two sulfur atoms are directly linked to one another, because we consider the nature of the sulfur-sulfur bond to constitute an important, still unsolved problem[2].

The apparently simplest chemical compound containing such sulfur-sulfur bonds in the molecule is, of course, elemental sulfur itself, to which indeed this progress report must be largely restricted.

We can follow the history of sulfur back to the days of Sodom and Gomorrah[3]. Nowadays, sulfur is a very cheap material which is available industrially with unusual simplicity, in a purity that is exceptionally high for an element, and in enormous quantities. The present annual world consumption of sulfur amounts to *ca.* 40 million tons. That, so far, only a negligibly small proportion of this production is used directly as the element is mainly because we still know and understand far too little about the properties of sulfur to be able to change them to meet selected practical ends. One typical example of this is that scientists are still in dispute about the "melting point" of sulfur (see Section 2).

2. Elemental Sulfur

2.1. General

What actually is sulfur? Is that a real question? Certainly not if we are content with the answer, trivial today, that it has the simplest stoichiometric composition conceivable, merely a series of atoms of mass number 16. This answer, however, clarifies only the centuries-long arguments about the "composition" of sulfur, whether this was a combination of one "fiery" principle with one "acid" principle, a matter that was very intimately connected with the development of chemistry from ancient times through alchemy to the present day[4]. Nevertheless, this answer is of no further help if we want to know more about sulfur than that it is an element. Actually, this element presents an extremely complicated chemical system which is still far from fully understood. According to the external conditions, that system comprises sulfur molecules each containing from at least two atoms to several hundred thousand, mixed together in great variety:

$$S_x (x = 2 \text{ to } \approx 10^6!)$$

We are dealing here with true dynamic equilibrium mixtures that change their molecular composition on dissolution and by formation of new chemical bonds.

In this connection let us note yet again a fundamental misunderstanding that is often injected at the beginning of chemistry teaching, namely that there is a difference in principle between chemical elements on the one hand and chemical compounds on the other. There is in fact no essential difference between compounds composed of atoms all of the same kind and those composed of atoms of different kinds. Except for the noble gases, all the elements are chemical compounds whose properties at any one time depend greatly on the nature of the bonding and/or on the molecular size in the "modification" under consideration. Consider, for instance, the pairs graphite—diamond, white phosphorus—black phosphorus, or ozone—molecular oxygen. In these cases chemical reactions change the properties—reactions whose study, with the resultant understanding and ability to influence the properties, have been neglected for a surprisingly long time. The interaction between atoms—whether they are the same or different plays no decisive role—is the main problem in chemistry, the questions namely: how do atoms react with one another by means of their electron shells? why do they do this? and how?

If we consider the system "elemental sulfur" from this viewpoint it immediately becomes clear that the apparently simple question asked at the beginning of this Section still cannot be answered at all completely. The main reason for this is the surprisingly well developed tendency and

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[**] Based on a Lecture to the General Meeting of the Gesellschaft Deutscher Chemiker in Karlsruhe on September 17, 1971, and to the Regional Meeting at Leverkusen on May 10, 1972.

ability of sulfur to combine with itself to form chains or rings; only carbon is superior in this respect. Sulfur atoms have six outer electrons, of which the two unpaired 3p electrons are used for covalent bonding to neighboring atoms (Fig. 1). It follows that the chains cannot be collinear but must be zig-zag.

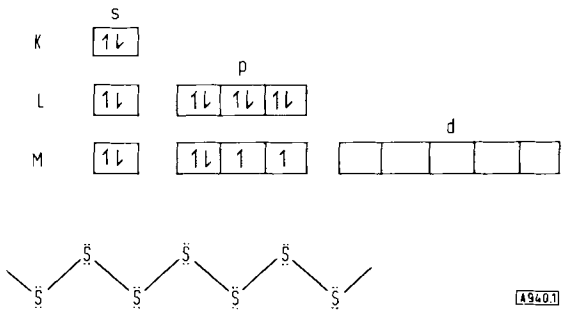


Fig. 1. Electronic configuration of a sulfur atom in the ground state; two-dimensional representation of a three-dimensional sulfur helix.

Such zig-zag chains are not planar because each sulfur atom has two further electron pairs which prevent free rotation around the sulfur-sulfur bond and thus produce a dihedral angle of $\approx 100°$. By dihedral angle is meant the angle formed by the planes each containing any two neighboring three out of four atoms in a section of the chain (cf. Fig. 2). According to whether we proceed upwards or downwards when passing from the third to the fourth atom in the first plane, we have the beginning of a right-handed or a left-handed helix:

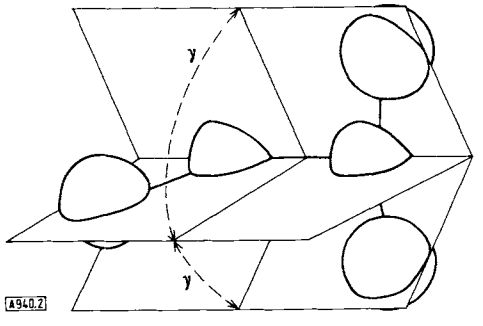


Fig. 2. Dihedral angle (γ) between any three neighboring of four sulfur atoms, which begin a right- or a left-handed helix.

Sulfur chains (and, of course, also sulfanes, *i.e.* compounds containing chains of sulfur atoms) thus have helical configurations. A helix with zero translation leads to a non-planar ring.

2.2. Well Known Sulfur Modifications

We shall now recapitulate briefly what textbooks usually teach about the system "elemental sulfur", this being often coupled with a general exposition of the concept of allotropy—an exposition that is only too frequently an example of how to kill any interest in the subject. To make matters worse, nowhere else in chemistry does one find such an incurably confused nomenclature as for sulfur: as if it were not enough that literally almost the whole Greek alphabet plus very honorable generic names have been misused to denote mixtures of largely unknown composition, hardly a single name has been used consistently for one material, and the same name has not seldom been used for different allotropic forms and for mixtures[5]. Most of this is better forgotten. Let us stick to the relatively few facts that are really firmly based. The most important fact is that, under normal conditions, only one compound of sulfur atoms is thermodynamically stable, namely the eight-membered cyclooctasulfur, S_8 (Fig. 3); for reasons mentioned above, this is not planar but has a crown form; it crystallizes in rhombs, which at 95.4 °C pass into monoclinic crystals.

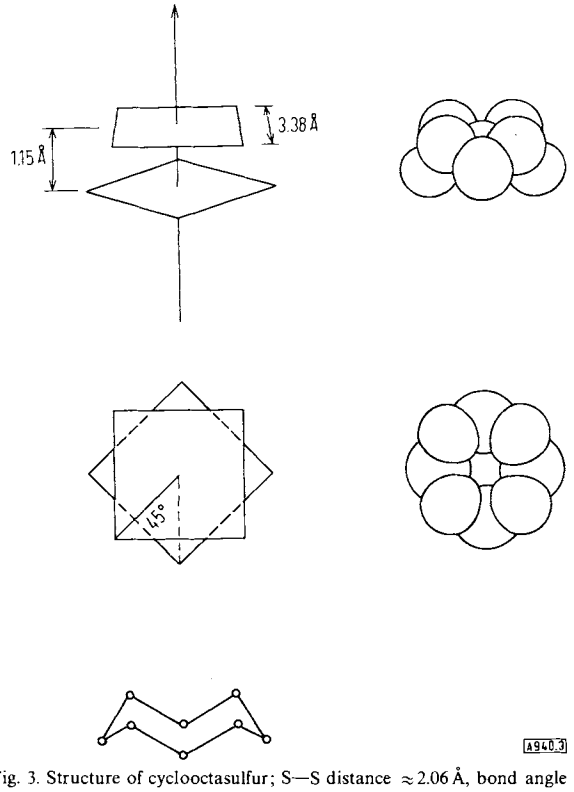


Fig. 3. Structure of cyclooctasulfur; S—S distance ≈ 2.06 Å, bond angle $\beta \approx 108°$, dihedral angle $\gamma = 98°$.

It is this cyclooctasulfur that we normally mean when we speak of sulfur. It is yellow—'sulfur-yellow'—but only at room temperature; at low temperatures it becomes snow-white. The color, or colors, of sulfur will be discussed below.

At ≈ 119 °C solid cyclooctasulfur passes into a pale-yellow mobile melt which, remarkably, solidifies again only at a temperature 4—5 °C lower than the melting point. This phenomenon, investigated so frequently and yet of old so unsuccessfully, has been ascribed to the difference between the "ideal" and the "natural" melting point of sulfur. Yet, precisely expressed, this means only that S_8 has not got a reversible melting point, but that at or below the melting point it decomposes partly to form other molecules which depress the solidification temperature.

Further heating of the sulfur melt leads at ≈ 160 °C to a peculiar phenomenon which we remember as a lecture experiment in our first term: the melt suddenly becomes very viscous and plastic; within a very narrow temperature range the viscosity increases by a factor of 2000! Further

heating slowly decreases the viscosity again, until at the boiling point of 444 °C the melt is again mobile, during which processes the color changes from pale yellow to deep red; sulfur can thus be not only white or yellow but also deep red! Finally, sulfur vapor is said to contain various molecules each containing an even number of atoms, namely S_8, S_6, S_4 and S_2.

If the temperature change is then slowly reversed, sulfur passes from the gas phase by way of the melt with its remarkable anomaly (now naturally in the reverse order) until at room temperature one has again cyclooctasulfur. If the melt is suddenly chilled from above 160 °C, the famous plastic sulfur is obtained—a still imprecisely understood mixture of components some soluble and some insoluble in carbon disulfide.

Somewhat "outside" this sulfur system lies cyclohexasulfur, S_6 (Fig. 4), known for 80 years as a barely considered laboratory curiosity:

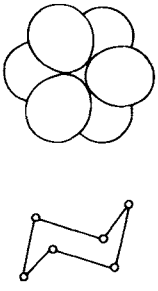
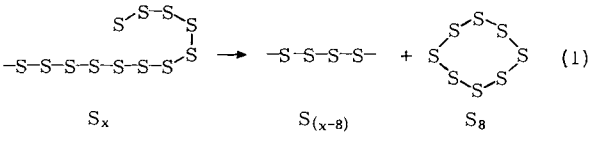


Fig. 4. Structure of cyclohexasulfur; S—S distance ≈ 2.06 Å, bond angle $\beta \approx 102°$, dihedral angle $\gamma \approx 75°$.

Its chair-shaped molecules form shiny orange-red crystals. This S_6, together with S_8, were until recently the only properly defined compounds containing only sulfur atoms. S_6 shows considerable ring strain in that it polymerizes already at ≈ 50—60 °C. Chemically it reacts with both nucleophiles and electrophiles in redox reactions that are up to 10000 times faster than those of S_8![6] Further, it is extremely sensitive to light. This is perhaps the place to mention the peculiar but generally disregarded fact that all sulfur-sulfur bonds are in principle sensitive to light, although this is quantitatively much dependent on the "strain" in the bonding. Even the most stable form of sulfur, S_8, polymerizes, for instance in benzene solution merely under the action of strong sunlight. The polymeric and chemically very reactive "photosulfur" thus formed depolymerizes rapidly in the dark, re-forming the eight-membered ring[7]. The mechanism proposed for this production of stable eight-membered rings from the longer chain molecules is that thermal movements and the preferred geometry of S_8 cause the terminal atom of a chain to attack always the eighth atom, with simultaneous formation of one sulfur-sulfur bond and cleavage of another.

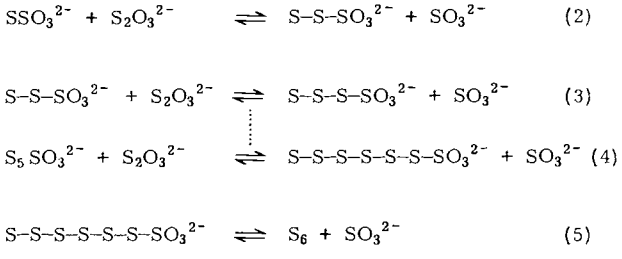


S_x $S_{(x-8)}$ S_8 (1)

Indeed, this "rolling up" of sulfur chains to rings is the reason why all compounds composed of sulfur atoms are converted finally into S_8[8].

Even quite feeble illumination converts S_6, either in solution or in the solid state, into S_8. For this change a direct reaction $4\,S_6 \not\rightarrow 3\,S_8$ is logically excluded; the six-membered rings that are breaking up must first form longer helical molecules, which then unwind so as to yield eight-membered rings in the manner illustrated above.

Current opinion is that exactly the opposite takes place, namely stepwise formation of sulfur chains during formation of S_6 (admittedly in rather poor yield) when thiosulfates are decomposed by mineral acids at low temperature, a reaction which was discovered already in the preceding century:



$SSO_3^{2-} + S_2O_3^{2-} \rightleftharpoons S\text{–}S\text{–}SO_3^{2-} + SO_3^{2-}$ (2)

$S\text{–}S\text{–}SO_3^{2-} + S_2O_3^{2-} \rightleftharpoons S\text{–}S\text{–}S\text{–}SO_3^{2-} + SO_3^{2-}$ (3)

$S_5SO_3^{2-} + S_2O_3^{2-} \rightleftharpoons S\text{–}S\text{–}S\text{–}S\text{–}S\text{–}S\text{–}SO_3^{2-} + SO_3^{2-}$ (4)

$S\text{–}S\text{–}S\text{–}S\text{–}S\text{–}S\text{–}SO_3^{2-} \rightleftharpoons S_6 + SO_3^{2-}$ (5)

In this reaction, polysulfanemonosulfonic acids (discovered earlier by us[9]) are formed starting from monosulfanemonosulfonic acid (thiosulfuric acid), the chain length increasing until it is long enough for the terminal sulfur atom to attack the other end of the chain, which it does by ring closure and extrusion of a sulfite ion[8]. This equilibrium reaction can be reversed by a sufficient excess of sulfite: there then occurs the familiar stepwise nucleophilic "sulfite degradation" of sulfur that leads to thiosulfate[9]. That in this special case the cyclohexasulfur can be separated from the main product S_8 is due to the very different solubility relations of the two modifications[10].

2.3. New Sulfur Modifications from Sulfanes and Chlorosulfanes

Since the nature of this modification, known previously as "Engel's sulfur" or "Aten's sulfur", was recognized, there has been no dearth of attempts to prepare sulfur rings other than S_8 and S_6; prior to our work, they were all unsuccessful. Also, there has been no lack of theoretical attempts to calculate and predict the stability or instability of hypothetical sulfur rings[11].

In view of this rather unsatisfactory situation we asked ourselves whether it might be possible to build new thermodynamically unstable compounds containing only atoms of one kind, *i.e.* new modifications of an element, by scientifically planned, kinetically controlled syntheses. This object would be the more easily achieved the fewer reaction steps were needed to combine precisely defined molecular units into the desired ring. Our first successes with this principle were when we used a two-stage redox reaction between sulfanes and chlorosulfanes:

$$H_2S_x + Cl_2S_y \longrightarrow 2\,HCl + S_{x+y} \quad (6)$$

$$\overset{-2}{H\text{–}S_x\text{–}H} + \overset{+2}{Cl\text{–}S_y\text{–}Cl} \longrightarrow \overset{0}{H\text{–}S_x\text{–}S_y\text{–}Cl} + HCl \quad (7)$$

$$H\text{–}S_x\text{–}S_y\text{–}Cl \longrightarrow HCl + \overset{S_x\ S_y}{\frown} \quad (8)$$

$$H_2S_4 + Cl_2S_2 \longrightarrow 2\,HCl + S_6 \quad (9)$$

In an open-chain sulfane the sulfur chain as a whole has the oxidation state -2, and in a chlorosulfane correspondingly $+2$. The overall reaction (6) is formally very simple, but for various reasons it is experimentally extremely difficult to realize it in such a way that pure sulfur is formed and not long-chain sulfanes or chlorosulfanes. It is essential to use the dilution principle, so that the unsymmetrically substituted intermediate product with a mean oxidation state ± 0 has the opportunity to split off hydrogen chloride when it assumes a suitable geometric orientation [reaction (8)].

We studied this procedure for the case of cyclohexasulfur [reaction (9)], whose properties were known. After an unstable modification of sulfur had thus for the first time become preparatively available in a pure form, we tackled the synthesis of new rings. From suitable components ($x+y$ in the general overall equation $= 12$) we then obtained the new sulfur modification cyclododecasulfur, S_{12}[12]. Contrary to *Pauling*'s prediction[13], this compound which crystallizes in pale yellow needles is disconcertingly stable; it "melts" appreciably higher than any other known form of sulfur, namely at 148 °C, although admittedly not reversibly but with decomposition. X-ray structure analysis showed the highly symmetrical form of the twelve-membered ring (Fig. 5), in which the atoms are arranged in three planes—six in the middle plane and three each symmetrically above and below it[14].

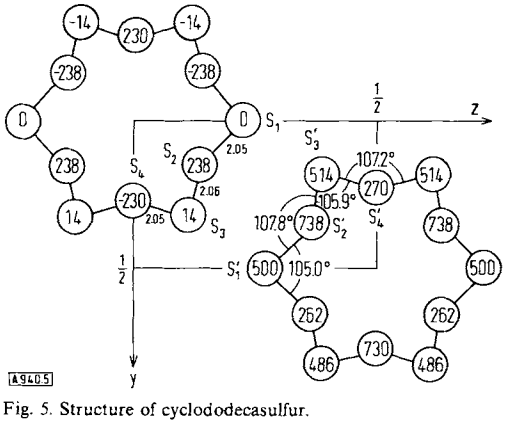


Fig. 5. Structure of cyclododecasulfur.

Like S_8, cyclododecasulfur S_{12} forms "regular" solutions in carbon disulfide, but its solubility therein is more than 150 times lower than that of S_8[10]. This unexpected solubility relation made it possible to separate the very stable new form from the large excess of S_8 and thus also to look for it in "normal" sulfur. And in fact cyclododecasulfur could be isolated from cooled sulfur melts, pre-heating to ≈ 120 °C being sufficient[15]. This finding throws a new light on the composition of sulfur melts, and their earlier interpretation thus requires reinvestigation, as will be briefly mentioned again below. As a small curiosity it may be mentioned here that small amounts of S_{12} crystallize out if saturated benzene solutions of S_6 are left for a short time in the light[6].

A rather stable cyclooctadecasulfur, S_{18}, which decomposes at 126 °C, and a cycloicosasulfur, S_{20}, with a decomposition temperature of 121 °C could also be obtained from sulfanes and chlorosulfanes[16]. Their interesting structures (Figs. 6 and 7) have been elucidated quite recently[16a, 16b]. Bond distances, bond angles and dihedral angles are similar to those in S_8 and S_{12}.

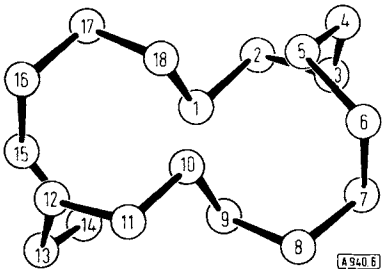


Fig. 6. Structure of cyclooctadecasulfur; S—S distance ≈ 2.06 Å, bond angle $\beta \approx 106°$, dihedral angle $\gamma \approx 85°$.

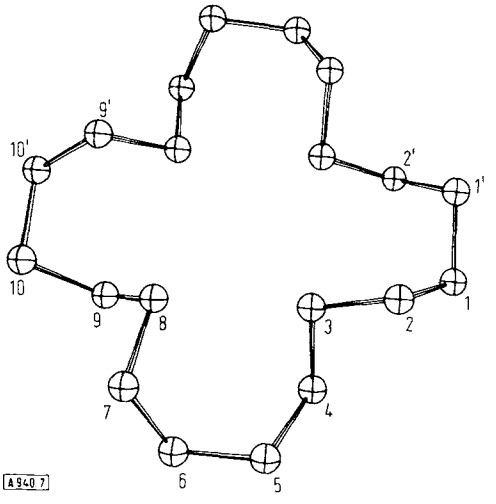


Fig. 7. Structure of cycloicosasulfur; S—S distance ≈ 2.04 Å, bond angle $\beta \approx 106°$, dihedral angle $\gamma \approx 85°$.

Our optimism about obtaining further relatively small sulfur rings by the procedure described was sadly damped by unexpected experimental difficulties. For example, it is almost impossible to carry out reactions with 100%-pure, homogeneous sulfanes, for the extremely unstable compounds of this class readily form equilibrium mixtures of various chain lengths, and these necessarily lead to various cyclic molecules, some of which are liquid at room temperature. Sulfur that is liquid at room temperature! an interesting phenomenon indeed, but once again only an indefinite mixture like the long-known melts. Because of the marked sensitivity of the strained rings to heat, light, or indeed even rough surfaces, all attempts at separation, *e.g.* chromatographically, have so far failed except when particularly favorable solubility relations prevailed, as between S_6, S_8, S_{12}, S_{18}, and S_{20}.

3. Sulfur Rings Containing Hetero Atoms

3.1. Rings Containing Metal Atoms

Out of this rather unhopeful position we found a way that brought us a few steps forward, namely by substituting for the sulfane a much more stable sulfur compound, of exactly defined composition, as starting material for the redox reaction that affords the sulfur rings.

A few years ago, when studying organometallic sulfur compounds, we synthesized a chair-form six-membered ring comprising five sulfur atoms and one titanium atom, where the metal atom carried also two π-bonded cyclopentadienyl ligands[17]. This bis(π-cyclopentadienyl)titanium pentasulfide (Fig. 8) is the prototype of a class of compound containing sulfur rings with a transition-metal atom as hetero atom; such compounds are under intensive study at the present time.

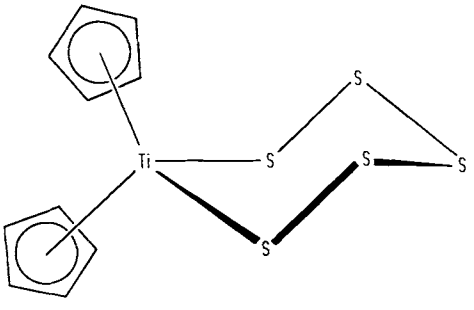


Fig. 8. Structure of bis(π-cyclopentadienyl)titanium(IV) pentasulfide.

It is interesting that at about the same time *Katz* and *Jones*[18] showed by X-ray structure analysis that this group includes a compound with the somewhat unusual stoichiometric composition $(NH_4)_2PtS_{15}$, known for almost 70 years but subjected to hardly any notice. In the PtS_{15}^{2-} ion the octahedrally coordinated Pt atom is the hetero atom in three chair-form six-membered rings, each of which contains five sulfur atoms whilst the Pt atom is common to all three rings—a structure that is hardly a daily occurrence in sulfur chemistry (see Fig. 9).

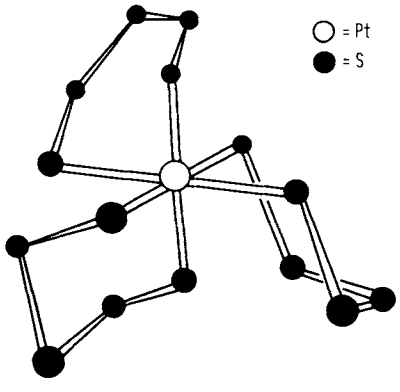


Fig. 9. Structure of the ion PtS_{15}^{2-}.

These remarkable metal-containing sulfur rings will not be discussed in detail here. However, one important question about their chemistry must be asked although it is not yet possible to give a convincing answer; it is this: Why, in these compounds, are ring sizes favored and stable that in wholly sulfur rings are very unstable or incapable of existence, as for example the six-membered sulfur rings mentioned above and—for molybdenum[19]—a five-membered ring containing four sulfur atoms and one metal atom? Consider our titanium compound (above): even conditions that we should expect to favor formation of other ring sizes always lead to formation of only the six-membered ring, which is apparently extremely favored; the permanganate-colored crystals melt only at 201 °C, indicating a thermal stability of sulfur chains that would have been inconceivable to a sulfur chemist a short time ago.

3.2. Rings Containing Methylene Groups

The question about ring size and stability applies not only to wholly sulfur rings but also to sulfur heterocycles other than those with transition-metal atoms. Two examples will suffice: As a model substance for cyclooctasulfur minus the sulfur-sulfur bonds we have built up a tetrameric thioformaldehyde[20] in which each second sulfur atom of the S_8 ring is replaced by an isoelectronic $-CH_2-$ group. In this series, the resulting 1,3,5,7-tetrathiacyclooctane, melting at 48 °C, is appreciably less stable than the well-known 1,3,5-trithiane which contains a six-membered ring; the former is readily converted irreversibly into a crystalline high polymer that melts undecomposed at 245 °C and corresponds to the unstable polymeric sulfur.

The powerful influence of the methylene group as "hetero atom" on the size of the more stable cyclic sulfur compounds has also been clearly shown in recent work by *Fehér et al.*[21]

3.3. Rings Containing Selenium Atoms

What do we observe if we insert sulfur's closest relative, namely a selenium atom, as hetero atom between sulfur atoms? Unlike sulfur, cyclooctaselenium is very unstable, changing spontaneously into the thermodynamically stable, high-polymeric selenium with a helical conformation. Why? We are not yet sure. What is the position with compounds containing both sulfur and selenium? At what stoichiometric composition do the stability relations between the eight-membered ring and the chain polymer "tip over"? Isolated attempts at an answer by melting the elements together in various stoichiometric proportions and mass-spectroscopic study of the gas phase above such mixtures do not lead us further here. We should bear in mind that, even for the (still hypothetical) eight-membered ring system comprising S_7Se to SSe_7, the conceivable different structural arrangements of these so closely related atoms can lead to more than 40 different isomers; we can then see clearly that only carefully planned syntheses, if any, will provide any possibility of isolating definite compounds as products. We have not made too remarkable progress in such investigations. Nevertheless, we now know three of the seven possible "stoichiomers"

containing an eight-membered ring, namely S_7Se, S_6Se_2 and S_5Se_3. As to the question about the influence of the hetero atoms on molecular size, it is significant that we can now say the following with certainty: In the sulfur-selenium system the sulfur is dominant up to a stoichiometry of at least 62:38 atom-% of sulfur to selenium. For, as in the wholly sulfur system, the (not yet realized) six-membered ring is certainly considerably less stable than the polymeric helix, which in turn changes again, spontaneously, into the thermodynamically most stable eight-membered ring.

Monoselenacyclooctasulfur, S_7Se, which presents no structural problem, was prepared by *Cooper* and *Culka*[22] from dichloroheptasulfane and hydrogen selenide by our synthetic method for chalcogen rings:

$$Cl_2S_7 + H_2Se \rightarrow 2HCl + S_7Se \quad (10)$$

We ourselves wanted to assess the possibility of existence of a six-membered ring of four sulfur and two selenium atoms by the reaction:

$$2Cl_2S_2 + 2H_2Se \not\rightarrow 4HCl + S_4Se_2 \quad (11)$$

but we had no success. Under the mild conditions sufficing for synthesis of cyclohexasulfur we always obtained as intermediate only a polymer of the same stoichiometry, thus:

$$2nCl_2S_2 + 2nH_2Se \rightarrow 4nHCl + (S_4Se_2)_n \quad (12)$$

This helix contained throughout its length a series of two sulfur atoms and one selenium atom. It very rapidly undergoes the reaction

$$(S_4Se_2)_n \rightarrow {}^2/_3 m S_5Se_3 + {}^1/_3 m Se_6Se_2 \quad (13)$$

yielding the new eight-membered rings S_5Se_3 and S_6Se_2 in the expected proportion 2:1 by the "rolling up" mechanism described in Section 2.2 for pure polymeric sulfur. Diselenacyclooctasulfur, S_6Se_2, forms lemon-yellow crystals melting at 124 °C; and triselenacyclooctasulfur, S_5Se_3, forms magnificent orange-red crystals melting at 120 °C; the difference in their solubilities is sufficient for them to be separable on a preparative scale and they are notably stable[23].

4. New Modifications of Sulfur from Metal-containing Sulfur Rings

After this excursion into the field of sulfur molecules containing hetero atoms we return to the desired rings containing atoms all of the same type. There we have got a little further by substituting the very stable titanium-sulfur six-membered ring for the very labile sulfanes in the redox reaction with chlorosulfanes described above. Bis(π-cyclopentadienyl)titanium(IV) pentasulfide reacts quantitatively with dichloromonosulfane, thus:

$$(C_5H_5)_2TiS_5 + SCl_2 \rightarrow (C_5H_5)_2TiCl_2 + 1/n(S_{6n}) \quad (14)$$

it affords di(π-cyclopentadienyl)titanium dichloride and sulfur, the latter being separable into 87% of cyclohexasulfur ($n=1$) and 11% of cyclododecasulfur ($n=2$)[24]. This gave us our first chance of synthesizing a ring with an odd number of members, by treating the titanium compound with dichlorodisulfane, S_2Cl_2, thus:

$$(C_5H_5)_2TiS_5 + S_2Cl_2 \rightarrow (C_5H_5)_2TiCl_2 + S_7 \quad (15)$$

Theoretical predictions made relatively small, odd-membered sulfur rings such as S_7 appear unlikely; if we exclude a planar ring with a uniform dihedral angle of 180°, which is impossible on bond-theoretical ground, we find that a seven-membered ring with equal bond lengths, bond angles and dihedral angles cannot be constructed. In spite of this, reaction according to eq. (15) occurs even under quite mild conditions[24]. Cycloheptasulfur crystallizes in yellow needles. It melts reversibly at 39 °C. X-ray structure analysis[25] has disclosed definite differences between the various dihedral angles. In the chair form of the seven-membered ring (Fig. 10) four atoms lie almost exactly in one plane. This therefore presents an element modification

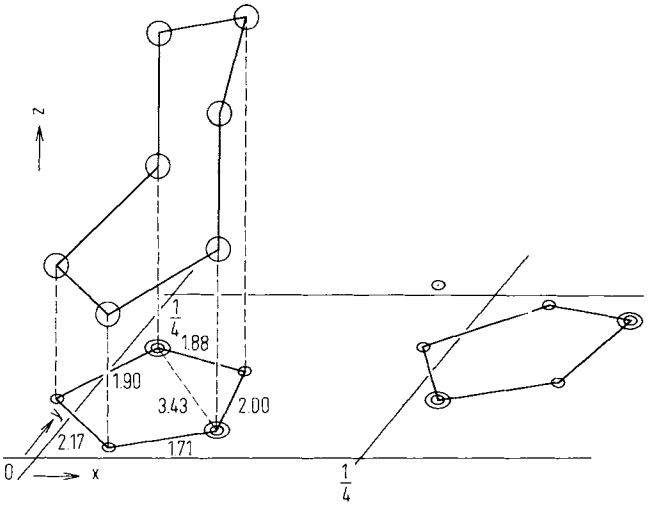


Fig. 10. Perspective view of a cycloheptasulfur molecule and its xy projection (bond lengths in Å).

in which identical atoms exist in differing electronic environments and thus have different energy contents. The ring strain is apparent in, *inter alia*, a notable sensitivity to light and heat: S_7 polymerizes even at *ca.* 45 °C; wherefore cycloheptasulfur can be kept for a long period only in the dark and the cold; even then it is converted slowly—to about 50% in a year—into a new insoluble but crystalline form of sulfur, the crystal structure of which has not yet been studied.

We have succeeded in preparing also a second ring containing an odd number of sulfur atoms, namely cyclononasulfur, from the titanium-sulfur ring and dichlorotetrasulfane[26]:

$$(C_5H_5)_2TiS_5 \xrightarrow{+HCl} (C_5H_5)_2Ti(Cl)S_5H \xrightarrow[-HCl]{+S_4Cl_2}$$
$$(C_5H_5)_2Ti(Cl)S_9Cl \rightarrow (C_5H_5)_2TiCl_2 + S_9 \quad (16)$$

Since the reactivity of chlorosulfanes decreases markedly with increasing chain length, S_4Cl_2 can no longer cleave the titanium-sulfur bond. We therefore made use of a trick: adding a small amount of hydrogen chloride cleaves the original ring, giving the sulfane derivative with five sulfur atoms, which, on reaction with S_4Cl_2, regenerates HCl and builds up a chain of nine sulfur atoms; and this cyclizes to the expanded nine-membered ring on elimination of the titanium dichloride complex. Its stability is about the same as that of S_6.

Very recently we have been successful in an analogous reaction with S_6Cl_2, thus:

$$(C_5H_5)_2TiS_5 + S_6Cl_2 \xrightarrow{HCl} (C_5H_5)_2TiCl_2 + S_{11} \quad (17)$$

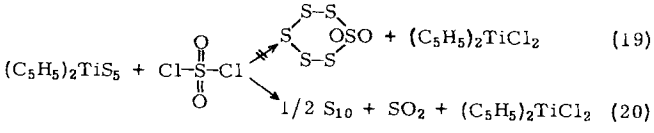
In this way we obtained cycloundecasulfur as the third compound with an odd-membered sulfur ring[27]. This new modification of sulfur can also be kept only in the dark and under cooling.

Are there also rings smaller than S_6? We do not yet know. From our experiments it appears anyway that if a pure cyclopentasulfur can be prepared at all it will be very unstable. Bis(π-cyclopentadienyl)molybdenum tetrasulfide which, as mentioned above, contains a five-membered ring of four sulfur and one molybdenum atom, reacts with SCl_2 thus:

$$(C_5H_5)_2MoS_4 + SCl_2 \rightarrow (C_5H_5)_2MoCl_2 + S_5\ (??) \quad (18)$$

The dichloro complex is formed together with elemental sulfur that is liquid at room temperature. The pronounced tendency of this sulfur to polymerize has so far prevented its characterization. The mass spectrum of a fresh sample did show a strong S_5^+ line, but along with mass lines of larger sulfur ions. We do not yet know, however, whether the latter were formed directly during the synthesis or as a result of polymerization[27]. The question of the existence of a five-membered sulfur ring is thus still open.

Next we may ask a question that has much interest from a bond-theoretical aspect: Are there well-defined sulfur rings with an oxidized sulfur atom of oxidation state +6 in the ring, *i.e.* with a sulfonyl group? According to our experiments to date we must answer this question in the negative. We may cite one example: if our compound with the titanium-sulfur ring is treated, not with SCl_2, but with sulfonyl chloride, the formation of a six-membered cyclic sulfone is conceivable:



however, apparently owing to the instability of a —S—SO_2—S— group, sulfur dioxide is split off, as in (20).

In this connection the result of recent experiments by *Steudel* is of particular interest. He succeeded in isolating cyclooctasulfur monooxide from the product of reaction of "crude sulfane" with thionyl chloride[28], thus:

$$H_2S_x (x \approx 4\text{—}6) + SOCl_2 \rightarrow 2HCl + S_8O + ? \quad (21)$$

This is the first sulfur-ring compound containing an oxygen atom bonded to it.

It is important also that reaction (20) does not give an isolable five-membered sulfur ring, but instead a further new sulfur modification, cyclodecasulfur[24], whose crystals resemble those of all the other new cyclic sulfurs, except S_{12}, S_{18} and S_{20}, in having little stability towards light or heat. Thus we now have the compounds S_6, S_7, S_8, S_9, S_{10}, S_{11}, S_{12}, S_{18} and S_{20} available for comparative study—a task that is still far from complete. The definite proof of their mere existence, however, throws up several questions about interpretation of the whole sulfur system to which I shall return briefly below. But first I shall insert a few remarks about charged sulfur molecules, some of which have aroused great interest in the last few years.

5. Charged Sulfur Molecules

The neutral sulfur molecules described in the preceding Sections change their nature in characteristic manners when either reduced to oxidation state −2 or oxidized to oxidation state +2.

It has been known for a very long time that cyclooctasulfur is reduced by sulfide or hydrogen sulfide ions to polysulfide ions S_x^{2-}, these naturally being partly protonated in water. The nucleophilic attack of S^{2-} ions on the electrophilically acting S_8 ring is the rate-determining step in that reaction:

$$S_8 + S^{2-} \rightarrow S_9^{2-} \quad (22)$$

The ring is broken to give the open-chain nonasulfide ion. Such open-chain polysulfide ions are rapidly degraded further (=further reduced) to shorter chains[29], for example thus:

$$S_9^{2-} + S^{2-} \rightarrow S_8^{2-} + S_2^{2-} \text{ or} \quad (23)$$
$$S_4^{2-} + S_2^{2-} \rightarrow 2S_3^{2-}, \textit{ etc.} \quad (24)$$

Such negatively charged sulfur ions can also be easily obtained free from water, for example by reduction of elemental sulfur by non-noble metals. They are all open-chain, doubly negatively charged fragments of a sulfur helix[30].

For an account of very recent interesting studies on the colored radical anions S_x^- see Ref.[30a].

In the reverse process, however, namely oxidation, the S_8 ring may under certain circumstances remain intact, though with a change of conformation.

As early as 1804[31] it was known that sulfur dissolves in oleum with formation of colored compounds—according to the conditions red, yellow or blue. The best known of these "compounds", the blue "S_2O_3", has been in the literature for nearly 100 years[32] and is mentioned in many textbooks even nowadays. S_2[33] and recently the radical ions $(X_2S{-}SX_2)^+$[34] or S_x^+[35] have also been made responsible for the colors. It is now regarded as proved that the various colors should be considered as due to the cations S_{16}^{2+}, S_8^{2+} and S_4^{2+}, and I must describe these briefly.

A solution of sulfur in oleum must contain other species in addition to these diamagnetic ions, for such solutions are paramagnetic, as has been known for 16 years[36]. The nature of these paramagnetic ions has not yet been finally decided. S_4^+, S_5^+, S_7^+ and S_8^+ have been discussed[37,38], the favorite in the most recent investigations being S_5^+.

The diamagnetic ions have been studied mainly by *Gillespie et al.*[39] who succeeded in oxidizing elemental sulfur to the red cations S_{16}^{2+} in various reactions[40–42]:

$$2S_8 + 3AsF_5 \rightarrow S_{16}(AsF_6)_2 + AsF_3 \quad (25)$$

$$2S_8 + 3SbF_5 \rightarrow S_{16}(SbF_6)_2 + SbF_3 \quad (26)$$

$$2S_8 + S_2O_6F_2 \rightarrow S_{16}^{2+} + 2SO_3F^- \quad (27)$$

The deep blue S_8^{2+} ion was obtained by further oxidation, thus:

$$S_8 + 3AsF_5 \rightarrow S_8(AsF_6)_2 + AsF_3 \quad (28)$$

$$S_8 + 5SbF_5 \rightarrow S_8(Sb_2F_{11})_2 + SbF_3 \quad (29)$$

X-ray crystal structure determination[43] showed that in this case the eight-membered ring remained intact, but that its conformation was changed from *exo-exo* (crown form of cyclooctasulfur) to *exo-endo* (Fig. 11).

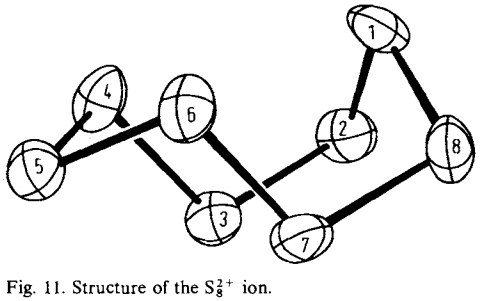
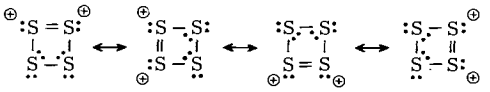


Fig. 11. Structure of the S_8^{2+} ion.

The average S—S separation (2.04 Å) in the doubly positively charged ring is identical with that in the neutral ring.

The pale yellow S_4^{2+} ion is obtained from S_8 and $S_2O_6F_2$ in liquid sulfur dioxide or from S_8 and SbF_5 at 150 °C. The compounds $S_4(SbF_6)_2$ and $S_4(SO_3F)_2$ are diamagnetic. Spectroscopic findings[44] provide compelling reasons for believing that, like Se_4^{2+} which has been defined by X-ray structure investigations[45], the cation S_4^{2+} exists as a planar "Hückel aromatic compound":



These charged sulfur molecules will keep research workers busy for some time yet and may be expected to provide many further interesting results. They will also exert an influence on our ideas about elemental sulfur itself, a subject to which I must now return.

6. Sulfur Vapor

First a few words about the gas phase above sulfur melts: This contains all possible fragments from S_8, and in addition traces of S_9 and S_{10}[30], as proved by mass spectrometry and contrary to statements in the textbooks mentioned above.

Blue S_2, *i.e.* blue sulfur, whose paramagnetism corresponds to that of the oxygen molecule, was obtained in a pure state by *Meyer* out of the gas phase under certain conditions, or better by photolysis of S_2Cl_2, and after being frozen in a matrix was very exactly characterized[46]. Recent results from *Ginsberg et al.*[47,48] should be noted here as of especial interest: these workers stabilized S_2—analogously to O_2—by π-bonding it to rhodium or iridium in phosphane complexes at room temperature (Fig. 12).

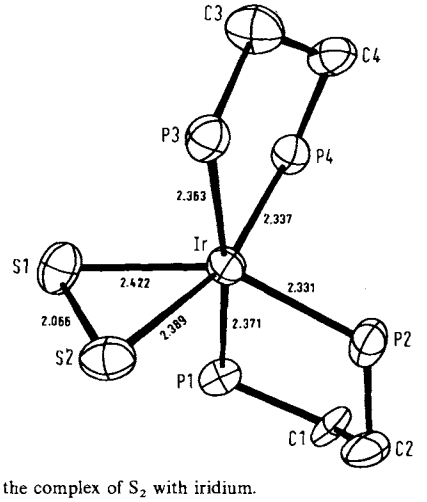
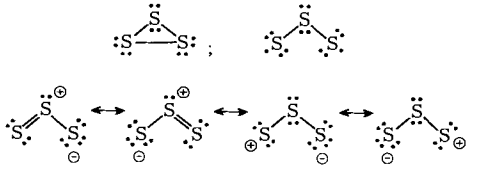


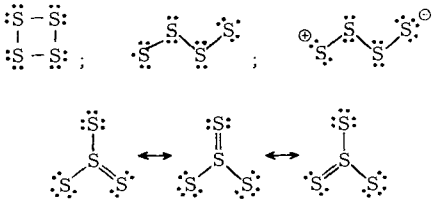
Fig. 12. Structure of the complex of S_2 with iridium.

But what do we know about the nature of the other components of the gas phase? The mass, *i.e.* the number of atoms, of the higher aggregates of S_3 tells us nothing at all. It seems an impermissibly crude simplification to regard the problem as solved by determining the masses of the aggregates of sulfur atoms that occur as positive ions in a mass spectrometer. Many problems merely begin at that stage! For example, is S_3 a ring, a diradical chain, a trithioozone or sulfur dithiooxide?



In this connection there is the interesting new observation that S_3 and S_4, obtained by photolysis of S_3Cl_2 and S_4Cl_2, respectively, in an organic glass correspond exactly in their absorption and thus in their colors—intense green and dark red, respectively—to the colors of hot sulfur melts and hot sulfur vapor. They do indeed cause the color of the melt and vapor[46].

To go a step further, what is the structure of S_4, which we know in the gas phase? Is it a ring, a diradical, a bipolar compound or a chain with double bonds? Recent HMO calculations[46] ascribed a completely unexpected, especial stability to a branched structure, namely sulfur trithiotrioxide.



This mathematical result certainly sets a challenge to the preparative chemist.

And we know absolutely nothing about the aggregates S_5, S_6, S_7, S_8, S_9, S_{10}, S_{11}, and S_{12} beyond that they have been shown to exist in the gas phase.

7. Sulfur Melts

We return now to the melts, which are surely the most complicated part of sulfur chemistry and about which we are still largely in the dark[49]. After many unsuccessful attempts to interpret their singular phenomena, the hypothesis of *Tobolsky* and *Eisenberg*, which has a most polished mathematical foundation[50], is nowadays generally adopted.

On this hypothesis a sulfur melt represents a reversible monomer-polymer equilibrium with cyclooctasulfur as the "monomer" which is *via* catenaoctasulfur in thermal equilibrium with high-polymeric *polycatena*sulfur, thus:

$$n\,S_{8\,(ring)} \rightleftharpoons n\text{—}S_8\text{—}_{(chain)} \rightleftharpoons (S_8)_{n\,(chain)} \qquad (30)$$

This interpretation can, however, no longer be maintained unchanged. The existence, in the melt, of sulfur compounds other than multiples of S_8 is proved unambiguously. The problem is thus open again and is the subject of renewed intensive theoretical study. According to *Semylen*'s more recent calculations[51], even at 120 °C, *i.e.* barely above the melting point, the mobile, pale yellow S_8 melt contains 8.2 wt.-% of larger rings containing an average of 13.8 atoms per ring. The "melting point" of sulfur is thus clearly a decomposition point and, by the theory of "regular solutions", we have estimated a true melting point of ≈ 133 °C for S_8[10]. At 120 °C the still mobile melt already contains almost 20% of rings with an average of 17.6 atoms per ring, and at 160 °C there should be 30% of larger rings.

What happens at the critical temperature where at a single stroke the melt suddenly becomes so viscous that the flask can be turned upside down without anything spilling out? We must admit that we do not yet know. Presumably we are then dealing with giant macromolecules. But why are they formed so suddenly and what is their structure? Are they rings or chains, and, if chains, are they diradicals or polar chains or do they contain fluxional double bonds? The problem of their conformation seems beyond hope when we remember that each time a chain is lengthened by one atom there are two equally justifiable alternatives for the new dihedral angle; thus simple calculation shows that there are $2^{(n-3)}$ (!) possibilities for each chain (n = the number of chain members), which gives about 130 possibilities for even 10 atoms and 9000 for 20 atoms; the theoretically possible conformations for molecules containing several hundred thousand atoms, such as may well exist in sulfur melts at ≈ 200 °C, run into astronomical figures.

Why do we nevertheless wish to clarify the situation? Well, because a knowledge of what happens in sulfur melts would enable us to influence their behavior and thus to multiply the practical applications of this substance that is so cheap and available in such huge quantities.

On continued heating, sulfur melts slowly become more mobile again and an increasingly deeper red until finally almost black-red. Because of thermal cracking of the macromolecules into smaller fragments the viscosity decreases up to the boiling point of 444 °C. The composition of the melt at this temperature is quite unknown. According to investigations by *Meyer*, the color becomes continuously more intense because, from the temperature of liquid air at which sulfur is snow-white, up to about 200 °C, there is a steady red shift of the absorption edge and thus of the absorption in the visible region, and this is caused by increasing thermal population of excited states of S_8 and later also by absorption due to higher polymers. The much stronger red shift of the absorption edge and thus the faster increase in color that finally occur at the higher temperatures—new absorption maxima appear at 4100 and 5300 Å—are to be ascribed to formation of S_3 and S_4 molecules which are present in a concentration of $\approx 2\%$ in hot polymeric sulfur and also cause the very intense color of the vapor[46]. The longer radical chains, analogous to the isoelectronic alkanediyl radicals, should be almost black. I cannot quite reconcile myself to the view that chilled, insoluble sulfur is again pale because the chain ends are saturated by impurities, for example hydrogen atoms, although that cannot be excluded—polymeric alkanes are, after all, colorless. However, cycloalkanes are also colorless! It seems thus more probable that "insoluble" sulfur consists of cyclic molecules which, as we know from the solubility relations of cyclododecasulfur, need not be all too large.

The proof that there are very reactive molecules such as S_3 and S_4 in sulfur melts throws a new light also on the very interesting reactions of hot sulfur with hydrocarbons, but I cannot go into that subject here.

A few words more about the much discussed "critical temperature" of sulfur. Our view is that, in principle, it cannot be determined. The prolonged dispute about the exact polymerization temperature, often treated as a matter

of the purity of the sulfur, is irrelevant today, as a few simple experimental results will show. First, however, an interesting interpretation of the conditions in sulfur melts should be mentioned, which was suggested several years ago but has been largely neglected[52]. *Wiewiorowski et al.* interpreted the conditions in sulfur melts on the basis that diradical sulfur chains form charge-transfer complexes with still unbroken S_8 rings as chain endings. Can we then imagine that, at the "critical temperature", the concentration of the eight-membered rings still present in the equilibrium mixture no longer suffices to stabilize the relatively short chains, so that these unite to give the macromolecules observed and thus cause the sudden increase in viscosity?

We are now familiar with highly viscous and therefore polymeric sulfur at temperatures as low as $\approx 45\,^{\circ}C$—this is the pale yellow polymerizate of cycloheptasulfur. Between 60 and 80 °C, S_6, S_9, S_{10}, and S_{11} form a similar polymerizate which on further heating to above $\approx 120\,^{\circ}C$ becomes mobile again and then once more plastic before, at 444 °C, it is once more less viscous and boils. However, we are also able to alter the "critical temperature" of "ordinary" sulfur by design: adding a mere $\approx 2\%$ of S_6 to sulfur melts at $\approx 150\,^{\circ}C$ lowers the polymerization temperature by $\approx 10\,^{\circ}C$—a phenomenon that lasts for *ca.* 20 minutes. And the opposite is also possible: we can prevent the polymerization of sulfur to highly viscous compounds up to at least 200 °C—*i.e.* retain sulfur melts in a mobile state—by adding as little as 1—2% of thermally stable, cyclic sulfur compounds such as trithiane or trimeric thioacetaldehyde. Do these rings take over the stabilizing role of the unstable S_8 rings in formation of complexes by sulfur chains? Anyway, they can be recovered from the sulfur unchanged and quantitatively[53]. At this point, however, I must break off speculation and thus also the discussion of liquid sulfur.

8. General Concluding Remarks

It is to be expected that the sulfur problem will continue to excite interest for a long time yet, even if no further groups of atoms are unrolled. Alone the future necessity, for prevention of environmental pollution, to remove sulfur dioxide from the combustion products of fossil fuels and, preferably, for practical reasons, to convert it into elemental sulfur[54], will have its effect on the price of sulfur: the world price of sulfur, which has varied for so long, will then settle down into a "valley" which will perhaps be deeper than has previously been assumed. This foreseeable development should encourage us to make a virtue of necessity! If by solving the environmental SO_2 problem we make sulfur into a new cheap material, what large quantities will be available! The following few, arbitrarily selected, potential uses, which we can only sketch here, are based on serious experiments in different laboratories: sulfur as a filler to modify organic polymers, as a covering for slow-acting fertilizers, as a material for marking streets, as an additive to improve the quality of bituminous material in road construction; and, finally, in the building industry—potentially a particularly important application—as a surprisingly stable mortar for conventional building stone, but also as a construction unit on its own if filled with sand or made into a foam; *etc.* The idea of a "front parlor" made of sulfur is certainly unusual, but that is not intended; we should think rather of the need that so often arises for urgent manufacture of prefabricated buildings units for disaster areas: heated sand, mixed with sulfur, would be ready for immediate use.

In this connection a final word on flammability. Several recent investigations have shown that adding a few percent of certain materials, such as styrene and maleic acid, reduces the flammability of sulfur drastically—sufficiently for practical use—and that conversely, even though it sounds like a paradox, adding sulfur to polystyrene or polyurethane foams considerably increases their fire-resistance[55]. The more we learn how to modify the mechanical and chemical properties of the system "elemental sulfur", the more varied will be its future applications as a raw material; and these modifications will be the more successful the more knowledge and understanding we have of sulfur.

Insofar as this report treats the results of our own School, thanks are due to the dedicated and skilled work of the following collaborators: Frau B. Jutzi, Dr. H. D. Block, Frau Dr. B. Block, Dr. G. Knippschild, Dr. H. Kopf, and Dr. E. Wilhelm, who has been engaged for the longest time and most intensively with elemental sulfur. Grateful thanks are offered for financial support from Bayer AG, the Fonds der Chemischen Industrie, the Deutsche Forschungsgemeinschaft and the Sulphur Institute Washington/London.

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Hydrazidinyl Radicals: 1,2,4,5-Tetraazapentenyls, Verdazyls, and Tetrazolinyls

By Franz A. Neugebauer[*]

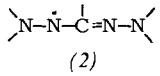
Dedicated to Professor Theodor Wieland on the occasion of his 60th birthday

This report reviews the preparation of hydrazidinyls and their chemical and physical properties.

1. Introduction

π radicals with allylic structure are often notable for their great stability, especially when the allylic system leads to an extensive, symmetrical delocalization of the unpaired electron. An historically interesting[**] example for such a stable allyl radical is (2,2'-biphenyldiyl)phenylallyl[1]. *Kuhn* and *Trischmann*[2] discovered a remarkably stable class of allylic radicals in the verdazyls *(3)*. These radicals are much more stable than the corresponding hydrazyls *(1)*[3], and in many cases even exceed the stability of the radical standard diphenylpicrylhydrazyl[4].

(1)



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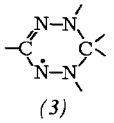

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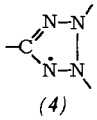

(4)

The discovery of the verdazyls has prompted the examination of other radicals having the same basic structure (*(2)* and *(4)*). We shall refer to this basic structural element as the *hydrazidinyl* system, in analogy to the nomenclature of the amidines and hydrazidines. The various representatives of this class are then *hydrazidinyls*.

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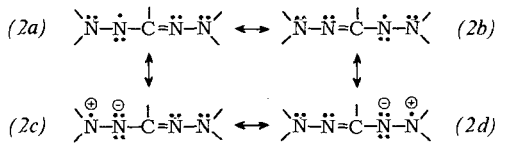
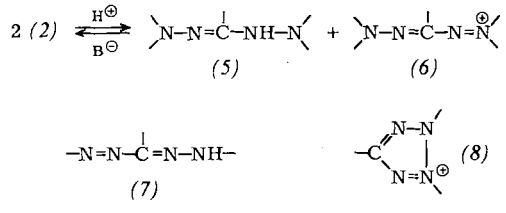
[**] The paper in ref. [1] was first submitted to J. Amer. Chem. Soc. for publication on June 9, 1932, but not accepted until April 10, 1957. The paper was rejected in 1932 because the general opinion was that the properties of the compound were incompatible with the structure of a carbon radical. The unequivocal proof of the structure with the ESR method was not possible until 25 years later.

2. The Hydrazidinyl System

The hydrazidinyl system may be described as a neutral azamethine system with an uneven number of methine groups and π electrons[5]: $7+2n$ π electrons and $5+2n$ atoms, with $n=0$. Because of the hydrazyl resonance *(2a)*↔*(2c)*, the free electron pairs of the outer nitrogen atoms are included in the π electron system. The relative weights of the resonance structures, and thus the spin density distribution, depend on the geometry of the hydrazidinyl system and on the nature of the substituents.



The linear hydrazidinyl system is realized in the 1,2,4,5-tetraazapentenyl radicals *(2)*[6]. In the verdazyls *(3)*[2], the hydrazidinyl system is forced into a *cis,cis* configuration, while the extreme case of directly bonded outer nitrogen atoms is found in the tetrazolinyls *(4)*[7-12]. 1,2,4,5-Tetraazapentenyls and verdazyls undergo a reversible disproportionation in the presence of acid[2,6], forming hydrazidines *(5)* and azacyanine cations (*(6)*; $4+2n$ π electrons and $3+2n$ atoms, $n=1$[5]). The basic structure is retained in this case. This is not so in the corresponding reaction of tetrazolinyls. The product formazan *(7)* has a different basic structure from *(4)* or the product tetrazolium ion *(8)*.

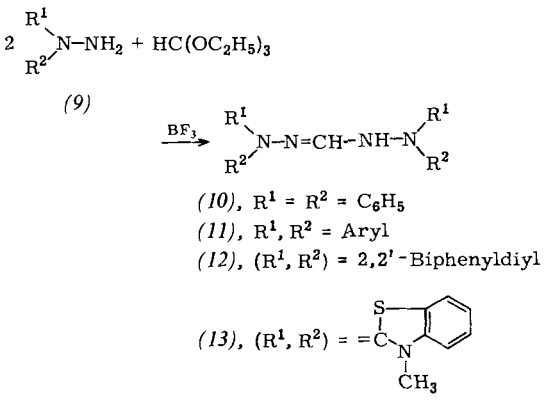


3. 1,2,4,5-Tetraazapentenyls

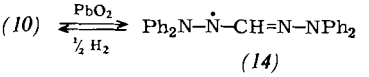
All known[6] open-chain hydrazidinyls are monomeric and have aromatic or other highly conjugated substituents on the outer nitrogen atoms. The parent compound, 1,1,5,5-tetraphenyl-1,2,4,5-tetraazapentenyl *(14)*, has been isolated as a pure crystalline substance.

3.1. Preparation and Chemical Properties

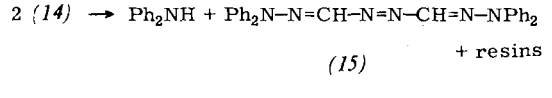
The synthesis of tetraazapentenyls starts with the colorless hydrazidines *(10)*—*(13)*, which can be prepared by the condensation of asymmetrically substituted hydrazines *(9)* with triethyl orthoformate in the presence of BF_3[6,13]. Solutions of *(10)*—*(13)* take on a intense blue-green color in the presence of air or, more effectively, upon addition of Ag_2O or PbO_2. Careful dehydrogenation of *(10)* with PbO_2 yields the hydrazidinyl *(14)*, which crystallizes as



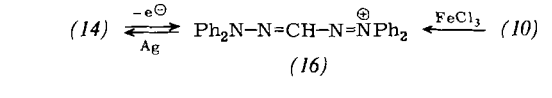
almost black prisms. The hydrogenation of *(14)* leads back to *(10)* with the absorption of 0.5 moles of H_2.



Pure crystals of *(14)* have a shelf life of several weeks. In solution, however, *(14)* decomposes within two days, as do the corresponding radicals from *(11)*—*(13)*. Cleavage of an N—N bond and recombination of the products leads to the orange-red azo compound *(15)*, diphenylamine (*via* the disproportionation of diphenylaminyl), and polymeric substances. *(15)* is also the main product of the thermal decomposition of *(10)* in boiling dimethylformamide (DMF). Radical *(14)* is an intermediate of the latter reaction.



The disproportionation of the tetraazapentenyls in the presence of acids is fully reversible if carried out with the exclusion of oxygen. Oxidizing agents such as halogens, $FeCl_3$, or $C(NO_2)_4$ remove the unpaired electron immediately from the radicals, forming the corresponding deeply colored tetraazapentadienium ions. These cations can be reduced to the radicals again with finely powdered silver. The azacyanine salts can be prepared by oxidation of the hydrazidines to the cations with $FeCl_3$ or $C(NO_2)_4$, followed by precipitation of the perchlorates with perchloric acid or of the double salts with $FeCl_3$ or $AuCl_3$.



3.2. Physical Properties

The symmetry of the π electron systems of tetraazapentenyls and azacyanine cations is demonstrated clearly by the absorption spectra. In the IR spectra, the νNH (3400 cm^{-1}) and νC=N (1650 cm^{-1}) bands of the hydrazidine *(10)* are replaced in the radical *(14)* by bands at 2100 and 2130 cm^{-1}. The latter are in the region of the allene and carbodiimide stretching frequencies and stem from the allylic system

$-\dot{N}-CH=N- \leftrightarrow -N=CH-\dot{N}-$

The radicals (640 nm) and the azacyanine cations (550 nm) both have strong bands in the visible spectral region, the exact positions being dependent on the nature of the outer substituents. Solutions of tetraazapentenyls obey Beer's law. According to susceptibility measurements, *(14)* is also monomeric in the solid phase (298—90 °K)[6].

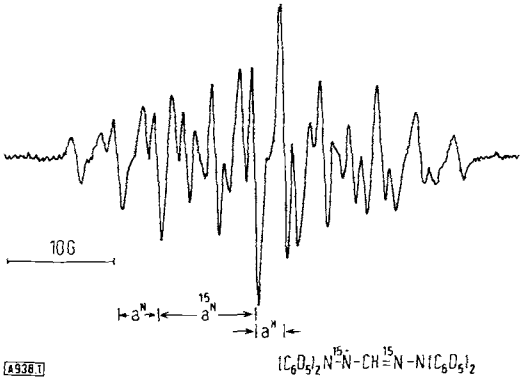
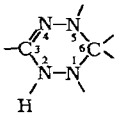


Fig. 1. ESR spectrum of 1,1,5,5-tetrakis(pentadeuteriophenyl)-[2,4-^{15}N]-1,2,4,5-tetraazapentenyl in benzene: $a^{N1,5}=3.73$, $a^{15N2,4}=9.06$, and $a^{HC-3}=2.63$ G.

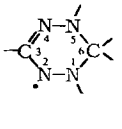
The analysis of the ESR spectra of selected substituted tetraazapentenyl radicals (cf. Fig. 1) yielded the following coupling constants for the backbone chain of *(14)*[14]: $a^{N1,5}=3.75$, $a^{N2,4}=6.5$, and $a^{HC-3}=2.76$ G. The large splitting of the nitrogens in positions 2 and 4 demonstrates clearly the allylic character of the tetraazapentenyl system, with high spin density at these positions. The g values of the tetraazapentenyls are all around 2.0036[14].

4. Verdazyls

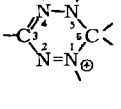
Because of the delocalized nature of the radical *(3)* and the cation *(18)*, the systematic nomenclature (*s*-tetrazine nomenclature[*]) of these systems, which requires a localized unpaired electron, becomes unprecise. Furthermore, the *s*-tetrazine nomenclature leads to long, unwieldly names and requires a renumbering of the atoms when going from the radical to the cation. On the other hand, the shorter and simpler verdazyl nomenclature proposed by *Kuhn* gives a better characterization of the paramagnetic resonance system, and will be adopted for this discussion.



(17): Leucoverdazyl (1,2,3,4-tetrahydro-*s*-tetrazine[*])



(3): Verdazyl (3,4-dihydro-*s*-tetrazin-1-(2 *H*)-yl[*])



(18): Verdazylium (5,6-dihydro-*s*-tetrazinium[*])

[*] Only this terminology is used in Chemical Abstracts.

The term leucoverdazyl will only be used in direct connection with verdazyls.

The geometry of the verdazyl backbone has been determined by X-ray diffraction analysis of 1,3,5-triphenylverdazyl[15]. The verdazyl ring takes on an unsymmetrical boat conformation (Fig. 2), in which the atoms in the conjugated system—including the phenyl substituents—are nearly coplanar. The phenyl groups on N-1 and N-5 lie only 9° and 12°, respectively, out of the plane of the nitrogen atoms, and are slightly twisted in anti-propeller fashion by 13° and 23°. In agreement with this picture of the verdazyl structure, NMR experiments on dissolved verdazyls indicate a hindered ring inversion[16].

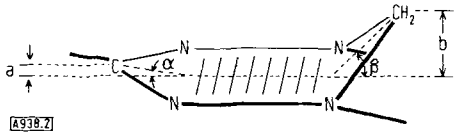
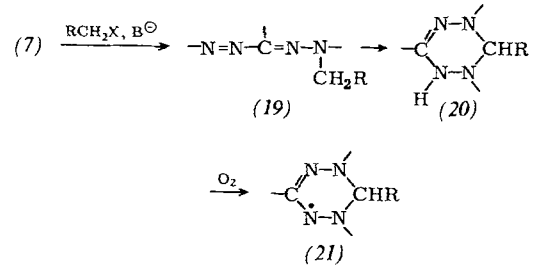


Fig. 2. The deviation of the verdazyl ring from planarity in 1,3,5-triphenylverdazyl: $a=0.099$ Å, $b=0.590$ Å; $\alpha=9.5°$, $\beta=42.9°$ [15].

The high stability of these radicals has made possible the synthesis of many mono-, bis-, tris-, and polyverdazyls, all of which are substituted on N-1 and N-5 with aromatic or equivalent conjugated groups. On the other hand, great variation of the substituents is possible in positions 3 and 6[2,16,17]. No case of dimerization of a verdazyl has been observed to date.

4.1. Preparation

Verdazyls were discovered during attempts to alkylate formazans[2]. It has been verified by experiment that formazans *(7)* are first alkylated to *N*-alkylformazans *(19)*. These compounds often cyclize at room temperature to yield leucoverdazyls *(20)*, which are then dehydrogenated by atmospheric oxygen to the verdazyls *(21)*. The procedure is simple: Formazan, alkylating agent, and base (BaO, $Ba(OH)_2 \cdot 8H_2O$) are stirred in an aprotic solvent (DMF) in the presence of air. Almost all formazans are alkylated under these conditions, but the choice of alkylating agents seems to be restricted to primary alkyl halides or dialkyl sulfates.



This reaction stops at the alkylformazan stage *(19)* if the formazan is only substituted at the 1,5 positions or if the substituents at these positions are of electron withdrawing nature (4-nitrophenyl, diphenylcarbamoyl)[2,18-20]. Two isomeric *N*-alkyl derivatives may be formed if the substrate has different substituents at posi-

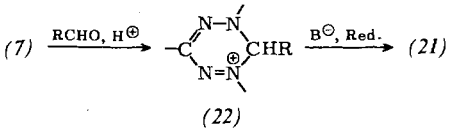
tions 1 and 5[20]. Stable *N*-alkylformazans rearrange to leucoverdazyls at higher temperatures (100 °C), and these can be dehydrogenated to the verdazyls with an equivalent amount of an oxidizing agent ($K_3Fe(CN)_6$[2], $FeCl_3$[16]).

The aminoalkylation of formazans also appears to be possible. The reaction of 1,3,5-triphenylformazan with formaldehyde and secondary amines yields verdazyls with dialkylamino groups at position 6[17], presumably *via* the intermediates *(19)* and *(20)* (R = 1-piperidyl, *etc.*).

Diazomethane has also been used as the alkylating agent in some special cases (*e.g.* 1,3-diphenyl-5-(2-benzothiazolyl)verdazyl[21]).

The alkylation procedure has also been used successfully for the preparation of bis-, tris-, and polyverdazyls[22], either *via* alkylation of bis-[23-25], tris-[23,26], and polyformazans[27,28], or by reaction of monoformazans with bifunctional alkyl halides[23,25] or with *p*-chloromethylpolystyrene[29].

Verdazyls can also be prepared easily by reacting formazans with formaldehyde[2]. In the presence of acid ($KHSO_4$, BF_3, HCl), formazans *(7)* condense with formaldehyde to yield verdazylium ions *(22)*, which are reduced to the verdazyls by an excess of aldehyde upon addition of base. Many mono- and bisverdazyls have been prepared in this manner[2,18,23,30-32]. Other aliphatic aldehydes (acetaldehyde, *etc.*) can be used in place of formaldehyde, but the method fails when aromatic aldehydes (benzaldehyde) are used.



(22)

Verdazyls are also formed in the reaction of formazans with formaldehyde in the presence of base and oxygen[2]. In this reaction the verdazyls are not formed directly, but are the products of an unknown reaction sequence[24].

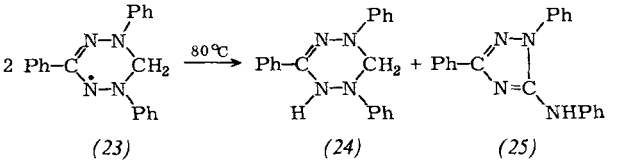
Reactions of verdazyls which leave the unpaired electron unchanged have found some use in special synthetic problems. For instance, aminoverdazyls can be acylated with acyl chlorides or converted into bisverdazyls with bifunctional acyl chlorides[33]. The reaction with aldehydes yields aldimines[24]. Polyverdazyls can be synthesized *via* polycondensation or polyaddition of a diaminoverdazyl with terephthalaldehyde, terephthaloyl chloride, or 1,4-phenylene diisocyanate[34]. Polyverdazyls (homo- and copolymers) can also be prepared by *anionic* polymerization of vinyl substituted verdazyls[35].

4.2. Chemical Properties

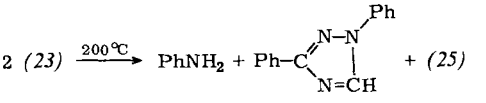
Crystals of the parent compound 1,5-diphenylverdazyl have a shelf life of a few weeks. The stability of derivatives increases with the nature of the substituent at C-3 in the following order: H[2] < CH_3[16] < $COOR$[18] < $C(CH_3)_3$[36], C_6H_5[2]. Verdazyls with *tert*-butyl or aryl substituents at C-3 remain unchanged over a period of years. The stability is evidently affected by the chemical reactivity of the group at C-3 (α- and β hydrogens) and by its ability to sterically shield the verdazyl ring. Replacing a hydrogen at C-6 by alkyl[16] or phenyl[2] groups also stabilizes the verdazyls[37].

With few exceptions, verdazyls are also stable for a period of weeks in dilute solutions. In saturated solutions, however, the radical concentration decreases considerably in a matter of days.

As with other stable radicals, disproportionation reactions become a key factor in such solutions. Keeping a saturated solution of 1,3,5-triphenylverdazyl *(23)* in benzene at reflux temperatures for a day yields 1,3,5-triphenylleucoverdazyl *(24)* and 5-anilino-1,3-diphenyl-1,2,4-triazole *(25)* in a 1:1 ratio[38]. Similarly, thermolysis of *(23)* at 200 °C produces aniline, 1,3-diphenyl-1,2,4-triazole *(26)*, and *(25)*[2,38]. Aniline and *(26)* are evidently the thermolysis products of *(24)*.

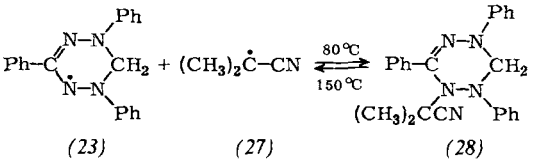


(23) (24) (25)



(26)

The autoxidation of benzaldehyde and the radical polymerization of vinyl monomers is inhibited by verdazyls, which are transformed to N-2 substituted leucoverdazyls *(29)*[2,39-42] in the process. The cyanopropyl radical *(27)* reacts with 1,3,5-triphenylverdazyl *(23)* in good yield (>60%) at temperatures below 100 °C[43]. The product of the combination reaction *(28)* dissociates again at temperatures above 100 °C, whereby *(29)* is consumed in side reactions, and the verdazyl *(23)* can be reisolated in high yield (77%). Thus, *(27)* can be used as an effective protecting group in the synthesis of verdazyls[33].

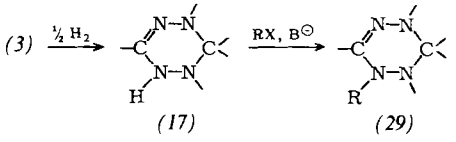


(23) (27) (28)

The green verdazyls *(3)* can be reduced to the colorless leucoverdazyls *(17)* by reducing agents such as $Na_2S_2O_3$, H_2S, dihydropyridines, ascorbic acid, *etc.* The mechanism of the hydrogen transfer from dihydropyridines to verdazyls has been thoroughly studied[44-47]. "Microhydrogenation"[48] is a convenient method of checking the purity of verdazyls[2,23], because the hydrogenation over a Lindlar catalyst or 5% $Pd/BaSO_4$ stops at the leuco compound after consumption of 0.5 moles of H_2[*]. The N—H group of leucoverdazyls *(17)* can be easily alkylated, *(17)* → *(29)*.

[*] Mononitroverdazyls take up 3.5 moles of H_2 to yield aminoleucoverdazyls.

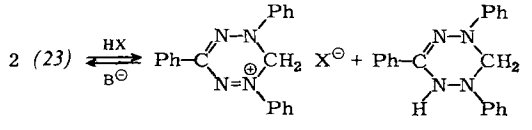
The *N*-alkyl derivatives *(29)* are sometimes formed in side reactions during the alkylation of formazans[2,36,49]. NMR studies indicate that a slow nitrogen inversion occurs in *(29)*[49].



(17) *(29)*

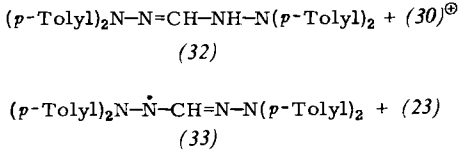
Verdazyls are oxidized immediately by halogens, $FeCl_3$, or $C(NO_2)_4$ to the corresponding verdazylium ions *(18)*, which can be isolated as the perchlorates or as the double salts ($FeCl_4^-$, $AuCl_4^-$, $PdCl_4^{2-}$, $PtCl_6^{2-}$)[2,31,50]. These cations are azacyanine dyes with *cis,cis* configuration of the methine chain. Substituents in the *para* position of the *N*-phenyl rings lead to a bathochromic shift of the first absorption band of the verdazylium ion *(30)* at 548 nm, regardless of the nature of the substituent (electron donor or acceptor)[31,50]. As might be expected, the bathochromic effect of electron donors is more prominent. The "mean value rule" for polymethine dyes[51] applies also to the verdazylium ions. Electron donating substituents in the *para* position of the *meso*-*C*-phenyl ring also effect a bathochromic shift of the first transition, while electron acceptors cause a small hypsochromic shift[50].

Verdazyls disproportionate in the presence of acids to form verdazylium ions *(30)* and leucoverdazyls *(31)*[2,30,52]. This reaction has been utilized in the form of a potentiometric titration for the quantitative determination of the radical concentration[28,29]. Leucoverdazyls are easily oxidized: atmospheric oxygen dehydrogenates *(31)* to *(30)* in weakly acidic solutions[2,30].



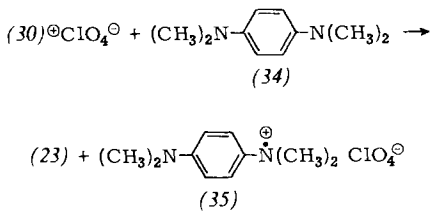
green *(30)* violet *(31)* colorless

Combined electron and proton transfer reactions may be observed if the redox potentials allow: 1,2,4,5-Tetraazapentene *(32)* and 1,3,5-triphenylverdazylium ion *(30)* react to form 1,2,4,5-tetraazapentenyl *(33)* and 1,3,5-triphenylverdazyl *(23)*[50].



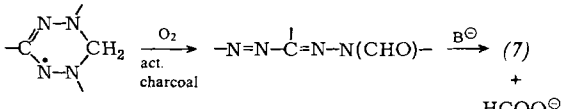
(32) *(33)*

Electron exchange reactions of two diamagnetic compounds to form two radicals are also possible in the absence of base, if the electron donating component reacts to form a radical cation. For example, the addition of verdazylium perchlorate *(30)* to a solution of tetramethyl-*p*-phenylenediamine *(34)* in benzene is followed by the precipitation of pure Wurster's blue *(35)* as the perchlorate[50].



(34) *(35)*

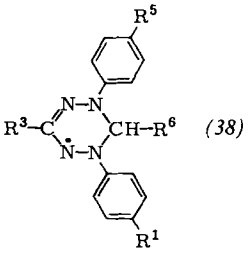
In the presence of activated charcoal, verdazyls with a methylene bridge in position 6 *(36)* are oxidized slowly to 5-formylformazans *(37)* by atmospheric oxygen. These formazan derivatives can be hydrolyzed with base to form formazans *(7)* and formate[37]. This oxidative ring opening, as well as the photochemical degradation of verdazylium salts[2], serves as a chemical proof of the fact that the backbone structure of the formazan chain is retained in the verdazyls.



(36) *(37)*

4.3. Physical Properties of the Monoverdazyls

In concurrence with the polymethine structure of verdazyls, the first electronic transition, which is almost independent of solvent, is found at about 700 nm. Extension of the conjugated system *(38)*, either by substitution in the *para* position of the *N*-phenyl rings (R^1, R^5) or in the *meso* position at C-3 (R^3), leads to a bathochromic shift of the longwave band—irrespective of the electron donating or withdrawing nature of the substituent. The bathochromic shift increases with various substituents in the following order: $R^1=R^5$ ($R^3=C(CH_3)_3$):H < $COOCH_3$, CN, OCH_3 < NO_2; R^3 ($R^1=R^5=H$):H < $C(CH_3)_3$ < CH_3 < C_6H_5 < 4-$C_6H_4OCH_3$ < 4-$C_6H_4NO_2$[24,31,50]. The "mean value rule"[51] for polymethine dyes is valid for verdazyls. The substituent R^6 does not take part in the conjugation system, but it can lead to a hypsochromic shift *via* steric interaction with this system. 1,3,5-Triphenylverdazyls with $R^6=C_6H_5$[2], NC_5H_{10}[17] exhibit a hypsochromic shift of about 20 nm in comparison with the parent compound. The electronic spectra of the verdazyls have yet to be satisfactorily interpreted within HMO theory[53].



(38)

The IR spectra of the leucoverdazyls have several bands in common which are characteristic of the structure: a sharp νNH band (3400 cm^{-1}), and a very strong ω phenyl band around 1600 cm^{-1}, which overlaps the much weaker νC=N band (the latter two bands are separated in the

2,4-^{15}N compound)[2, 14]. Many bands in the IR spectrum of 1,3,5-triphenylverdazyl are shifted by ^{15}N labeling (see Table 1). The small wave numbers of these bands in comparison with that of a pure νC=N absorption (1600 cm^{-1}) demonstrates that, as was to be expected, the *cis,cis* hydrazidinyl system is a strongly coupled system. An analysis of the vibrational system has not yet been reported[54, 55].

Table 1. Bands [cm^{-1}] in the IR spectrum of 1,3,5-triphenylverdazyl which are shifted by 2,4-^{15}N substitution [24].

CCl_4 Solution				KI Disk			
^{14}N	^{15}N	Δ	E_{rel} [a]	^{14}N	^{15}N	Δ	E_{rel} [a]
1394	1390	4	0.45	1390	1387	3	0.52
1368	1356	12	0.05	1367	1356	11	0.22
1255	1245	10	0.35	1262	1254	8	0.59
1134	1125	9	0.70	1142	1132	10	0.74
1117	1109	8	0.35	1117	1109	8	0.45
943	926	17	0.05	942	920	22	0.15 (s)
				799	796	3	0.02
652	647	5	0.25	649	644	5	0.45
600	597	3	0.35	600	598	2	0.45
				568	561	7	0.02
				443	441	2	0.07
				426	421	5	0.07

[a] Extinctions relative to the strongest band of the spectrum ($E_{rel}=1$).

Verdazyl solutions obey Beer's law. The monomeric nature of dissolved verdazyls has also been confirmed by NMR susceptibility measurements[56]. The paramagnetic susceptibilities of crystalline verdazyls obey the Curie-Weiss law over a wide range of temperatures[23]. Spin compensation due to exchange interactions is observed only at temperatures under 30°K[57]. The measurement of the *ortho-para* hydrogen conversion rate in the presence of verdazyls demonstrated experimentally that the specific rate constant is not only dependent on the magnetic moment of the added radical, but also on its molecular structure[58].

The typical ESR spectrum of verdazyls has nine lines or line groups in the intensity ratio 1:4:10:16:19:16:10:4:1. The coupling constants a^N of the four nitrogen atoms of the verdazyl ring are all about 5—6 G[2].

The proton coupling constants in the parent compound 1,5-diphenylverdazyl can be determined by comparison with the more highly resolved spectra of selectively substituted derivatives[18]. The splitting $a^{N1,5}$ is influenced by the nature of the substituent in the *para* position of the *N*-phenyl ring. The effect can be correlated with the Hammett relationship[31]. The *g* values of the verdazyls are around 2.0034.

The magnitudes and signs of the HFS coupling constants can also be determined from the paramagnetic shifts in the NMR spectra of free radicals[59]. This method has been applied to the stable monomeric verdazyls with great success (*cf.* Fig. 3). Both ^{1}H and ^{2}H HFS coupling constants of many verdazyls could be determined and unequivocally assigned using this method[16, 60-62]. In addition, the temperature dependence of the C-6 methylene proton resonance demonstrated the presence of an inversional equilibrium in the verdazyl ring in solution[16]. The dynamic nuclear polarization in verdazyl solutions has also been studied[63].

The spin densities of the verdazyls—from NMR and ESR data—are comparable with the calculated *(McLachlan)*

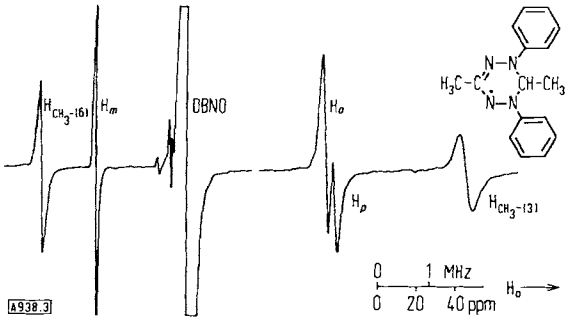


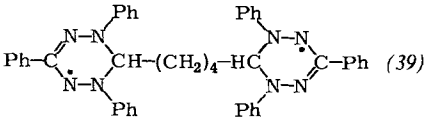
Fig. 3. The ^{1}H-NMR spectrum of 3,6-dimethyl-1,5-diphenylverdazyl in di-*tert*-butyl nitroxide (DBNO) [16].

spin density distributions of 1,5-diphenyl- and 1,3,5-triphenylverdazyl[53, 61]. The greater part of the free spin (≈80%) is distributed almost equally among the four nitrogen atoms of the verdazyl ring. Thus, the resonance structures *(2a)* and *(2c)* of the hydrazidinyl system have about equal weight in the verdazyls.

4.4. Physical Properties of Bis- and Trisverdazyls

Verdazyl moieties can be linked together at the ring positions N-1, C-3, N-5, and C-6. Nearly all known bis- and trisverdazyls fall into three groups, namely those linked symmetrically at N-1,N-1'-, at C-3,C-3'- and at C-6,C-6'.

A typical example for C-6,C-6' coupling is the bisverdazyl *(39)*[23]. The absorption spectrum of *(39)* is identical to that of the component verdazyl moieties. Susceptibility measurements over a wide temperature range yielded a value of 2.45 μ_B. The ESR spectrum at ambient temperature shows only one broad signal, but at reduced temperatures a dipolar zero-field splitting of $D=25$ G can be observed[62]. Thus *(39)* is a diradical with an almost degenerate singlet-triplet ground state. As is to be expected, the HFS coupling constants—determined in the ^{1}H-NMR spectrum—are half as large as those in the monoverdazyls[62].

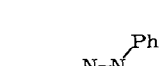


(39)

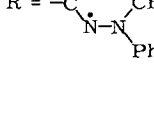
C-3,C-3' coupling of the verdazyl moieties through a conjugated bridge yields diffuse π electron systems with more than one unpaired electron. Prominent examples are the bisverdazyl *(40)* and the trisverdazyl *(41)*[23]. The ESR spectrum of *(40)* at ambient temperature shows signs of hyperfine structure ($a^N=2.8$ G). Two independent measurements of the zero-field splitting at 77°K have been reported: $D=43.1$ G[64] and $D=45$ G, $E=2$ G[62]. The ^{1}H-NMR spectrum yielded the coupling constant $a^H=0.12$ G for the protons of the bridging phenyl ring, while the splittings of the *N*-phenyl protons are about half as large as in the corresponding monoverdazyl[62]. These results and also susceptibility measurements (298–77°K) lead to the conclusion that the ground state of *(40)* is a nearly degenerate singlet-triplet state. Susceptibility measurements

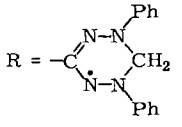
on the trisverdazyl *(41)*, which were carried out over a wide temperature range in solution and in the solid state, gave a value of $3\,\mu_B$. The ESR spectrum of *(41)* at ambient temperature shows hyperfine structure ($a^N = 2$ G). The analysis of the low temperature ESR spectrum yielded the zero-field parameter $D' = 28.5$ G. Thus, the trisverdazyl *(41)* has a nearly degenerate doublet-quartet ground state[65].

(40)



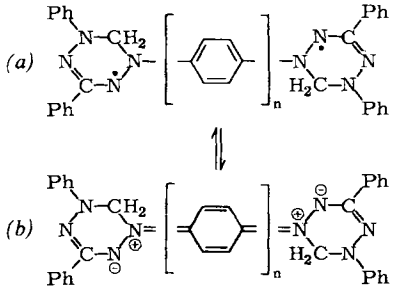
(41)





N-1,N-1′ coupling of verdazyl systems through conjugated bridges also leads to diffuse π electron systems, for example *(42a)*—*(44a)*[23,66]. The ESR spectra of these bisverdazyls at ambient temperature show hyperfine structure ranging in strength from very weak (*(42a)*) to strong (*(43a)*, *(44a)*), $a^N = 2.8$ G. The susceptibility values (298–90 °K) of *(43)* and *(44)* in the solid state correspond to degenerate singlet-triplet states. On the other hand, *(42)* has a lower molecular susceptibility, which decreases as the temperature is reduced. The absorption spectrum of *(42)* at ambient temperature (Fig. 4) shows in addition to the usual verdazyl bands a new band at 550 nm. This additional band becomes stronger at reduced temperatures, while the band at 440 nm becomes weaker. The process is reversible. This reduction in the concentration of bisverdazyl and in the paramagnetic susceptibility at low temperatures must be due to an intramolecular process, because the absorption spectra are independent of concentration. The unpaired spins of *(42a)* form a new double bond to the bridge, resulting in a diamagnetic, double zwitterion with a quinonoid bridge *(42b)* similar to the central structural element of Chichibabin's hydrocarbon. Increasing the length of the bridge tends to stabilize the bisverdazyl relative to the diamagnetic form. Thus in the low temperature spectrum of *(44)*, the band due to the diamagnetic zwitterion *(44b)* can only just be identified as a shoulder (Fig. 5). According to the susceptibility measurements and the ESR data, the bisverdazyls *(42a)*—*(44a)* are characterized by closely lying singlet and triplet states.

(a) ⇌ *(b)*



(42), n = 2
(43), n = 3
(44), n = 4

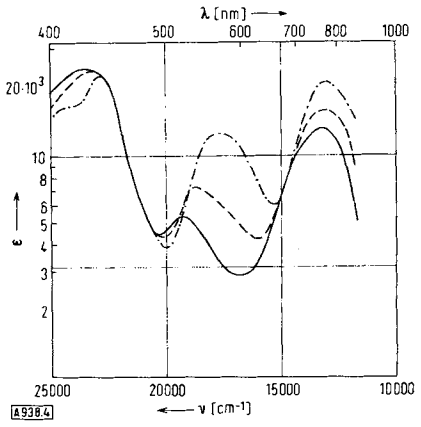


Fig. 4. Absorption spectrum of 4,4′-biphenyldiyl-bis[1-(3,5-diphenylverdazyl)] *(42)* in tetrahydrofuran/methylcyclohexane/diethyl ether/*i*-pentane (1:1:2:1) at 298 °K: ——, at 197 °K: – – –, and at 97 °K: – · – · – (corrected for volume contraction).

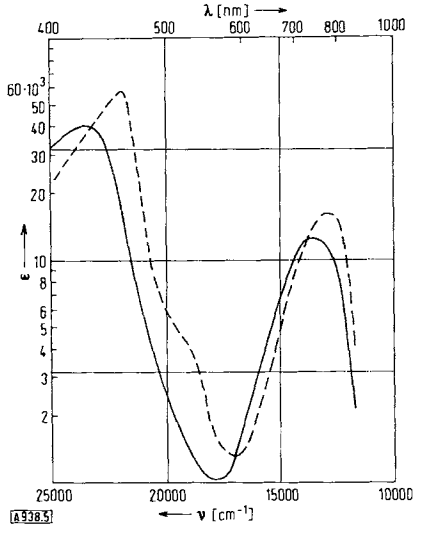


Fig. 5. Absorption spectrum of 4,4‴-quaterphenyldiyl-bis[1-(3,5-diphenylverdazyl)] *(44)* at 298 °K: ——, and at 97 °K: – – –; solvent as in Fig. 4.

5. Tetrazolinyls

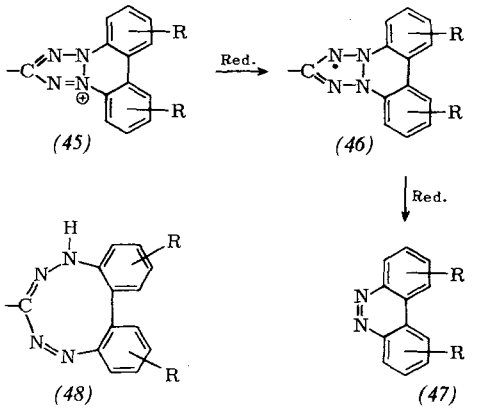
In tetrazolinyls *(4)*, the outer nitrogen atoms of the hydrazidinyl system are directly coupled to each other. Many "phototetrazolinyls"[*] *(46)* are isolable[67–70], but only one example *(50)* of a simple tetrazolinyl has been isolated to date[70,71]. All known tetrazolinyls are monomeric and are substituted on N-2 and N-3 by aromatic or other highly conjugated groups.

5.1. Preparation and Chemical Properties

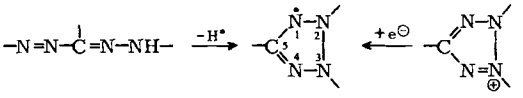
The reduction of phototetrazolium salts *(45)* with sodium amalgam, sodium dithionite, or sodium stannite led to the discovery and isolation of the first radicals of tetrazolinyl type[7,67–69]. The preparation is still restricted to this approach, because the lower oxidation state of the radicals,

[*] Derived from phototetrazolium ions; 2,3-(2,2′-biphenyldiyl)tetrazolinyls or 1*H*-benzo[c]tetrazolo[2,3-*a*]cinnolin-1-yls.

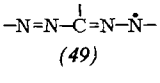
the cycloformazans *(48)*, have not yet been prepared[72]. The reduction of the phototetrazolinyls leads only to degradation products, *i.e.* benzo[*c*]cinnolines *(47)*.



As demonstrated by the strong ESR signals of the solutions, tetrazolinyls *(4)* are formed by reduction of tetrazolium ions *(8)* with potassium stannite[8], propiophenone anion[10], or silver amalgam[11], by dehydrogenation of formazans *(7)* with atmospheric oxygen[9,10] or lead dioxide[73], or by comproportionation of formazans and tetrazolium salts in basic medium[10]. The dehydrogenation of formazans to tetrazolinyls with di-*p*-tolylaminyl proceeds under very mild conditions[12]. Using this reaction, 5-*tert*-butyl-[70] and 5-phenyl-2,3-bis(4-nitrophenyl)tetrazolinyl[14] can be prepared and isolated. The dehydrogenation of bisformazans leads to mono- and bistetrazolinyls, as was demonstrated by ESR spectroscopy[73].

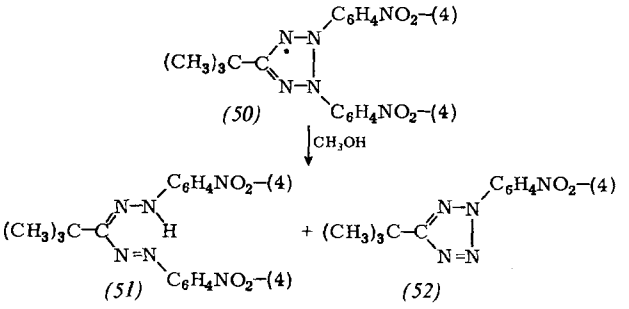


The oxidation state intermediate between formazans and tetrazolium ions might be formulated as the 1,2,4,5-tetraazapentadienyl radical *(49)*. However, ESR measurements have unequivocally identified the radicals as being tetrazolinyls and not the open-chain valence isomers[12,74,75]. Presumably, tetraazapentadienyls are the first products of the dehydrogenation of formazans. These intermediates, however, are not identifiable and evidently rearrange immediately to the more stable tetrazolinyls.



(49)

The stability of the tetrazolinyl radicals, which are inert towards oxygen under normal conditions, increases with increasing electron acceptor character of the *p*-substituents of the *N*-phenyl rings. Nitro-substituted tetrazolinyls *(50)* and cyano-substituted phototetrazolinyls are the most stable examples[70]. If care is taken to exclude light, CO_2, and water vapor, the crystalline radicals can be kept for months without decomposing. In weakly acidic medium (methanol), tetrazolinyl *(50)* decomposes immediately, forming formazan *(51)* and tetrazole *(52)*[70]. Under the same conditions, phototetrazolinyls yield benzo[*c*]cinnolines *(47)*. The reduction of phototetrazolinyls also leads to *(47)*. Conversely, tetrazolinyl *(50)* can be reduced to the formazan *(51)* with sodium dithionite. The oxidation of the tetrazolinyls and phototetrazolinyls with bromine or iodine proceeds with quantitative yield to the corresponding tetrazolium ions[67,70].

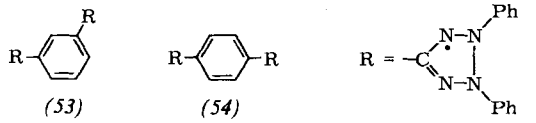


5.2. Physical Properties

In keeping with the tetracyclic conjugation system, the absorption spectra of the phototetrazolinyls have many bands in the UV range and a characteristic long-wave band at 600—700 nm. This band undergoes a bathochromic shift when the *N*-phenyl rings are substituted in the *para* position: H (608 nm), CH_3 (625 nm), CN (695 nm)[70]. Tetrazolinyl *(50)* has a long-wave band at 590 nm.

The experimental susceptibility values of tetrazolinyl *(50)* and several phototetrazolinyls are almost equal to the theoretical values for monoradicals. The Curie-Weiss law is valid over a wide temperature range (298 – 80 °K)[70,76]. These radicals are also monomeric in solution down to 70 °K (low temperature absorption spectra).

The ESR spectra of the tetrazolinyls have a nine-line hyperfine structure[8-12]. The coupling constant $a^{N2,3}$ (6.1—8.65 G) is distinctly larger than $a^{N1,4}$ (5.4—5.8 G), and is highly dependent on the nature of the *p*-substituents of the *N*-phenyl rings. The changes in $a^{N2,3}$ obey the Hammett equation[12,70,74]. In addition to the nitrogen coupling constants, high resolution ESR spectra of selectively substituted tetrazolinyls also yield the proton coupling constants of the parent compound 2,3-diphenyltetrazolinyl[74]. Similarly, the analysis of the highly resolved ESR spectra of selectively substituted phototetrazolinyls yielded $a^{N2,3}$ (6.3—7.8 G), $a^{N1,4}$ (3.75—3.9 G), and all hydrogen splittings of the parent compound 2,3-(2,2'-biphenyldiyl)-tetrazolinyl[75]. The *g* values of the tetrazolinyls are around 2.0037, and those of the phototetrazolinyls about 2.0036.



(53) *(54)*

Low temperature ESR spectra of the bistetrazolinyls *(53)* and *(54)* yielded the zero-field parameters $D = 51.6$ G and 37.9 G, respectively[73].

The spin densities—obtained from the ESR data of the radicals—are in satisfactory agreement with the calculated *(McLachlan)* spin density distribution for the tetrazolinyl structure. The ratio of the nitrogen coupling constants $a^{N_2}:a^{N_1}$ in the hydrazidinyl system goes from 1.7 in the tetraazapentenyls through 1.0 in the verdazyls to 0.75 in the tetrazolinyls and 0.5 in the phototetrazolinyls. In contrast to the allylic tetraazapentenyls, the major spin density in the tetrazolinyls is found on the outer nitrogen atoms of the hydrazidinyl system. This spin is partly delocalized into the *N*-phenyl rings by electron withdrawing substituents. The most stable tetrazolinyl *(50)* has almost equal coupling constants for all nitrogen atoms. This example demonstrates clearly the importance of optimal delocalization of the unpaired electron for the stability of free radicals.

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Bredt Compounds and the Bredt Rule

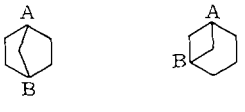
By Gert Köbrich[*]

Dedicated to Professor Theodor Wieland on the occasion of his 60th birthday

The Bredt rule, which proved useful in earlier decades mainly as an exclusion criterion in the assignment of structures, has in recent years become the stimulus for efforts to synthesize strained bicyclic systems with a bridgehead double bond. On the basis of the ring-strain forces operating in such systems, an extended Bredt rule is discussed. The "Bredt compounds" to which this rule applies, which include bicyclic systems not previously considered from this point of view (*e.g.* bridged methylenecyclopropanes), form a clearly circumscribed, interesting field within the chemistry of highly-strained hydrocarbons with ring unsaturation.

1. Introduction

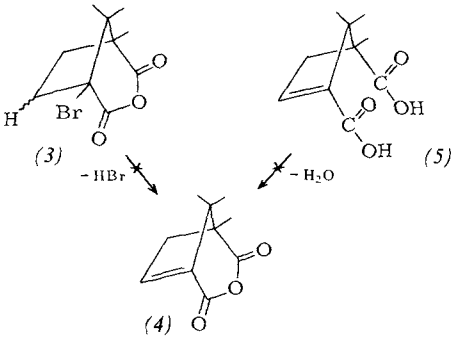
According to the rule formulated by *Bredt* and called after him, "in systems of the camphane and pinane series and related compounds *(1)* and *(2)*, the branching points A and B of the carbon bridges (the bridgeheads) cannot be involved in a carbon double bond"[1].



(1)

(2)

An experimental observation that led *Bredt* to this realization shortly after the turn of the century will be outlined here[2]. Firstly, the attempted dehydrobromination of the anhydride *(3)* was unsuccessful, whereas the corresponding dicarboxylic ester could be smoothly dehydrobrominated; secondly, the unsaturated dicarboxylic acid *(5)* was found to be incapable of forming its internal anhydride *(4)*, whereas saturated analogs underwent this cyclization very readily. The resistance to the formation of *(4)* and related bicyclic structures was correctly attributed by *Bredt* to the ring strain that would necessarily result from the distorted geometry of the carbon double bond at the bridgehead in comparison with normal olefins.



The correctness of *Bredt*'s hypothesis was soon shown very impressively by the fact that it was found necessary to revise all earlier structural assignments contrary to his postulate[3]. The Bredt rule therefore initially served, and still serves, as an exclusion criterion in the determination of constitutions of unsaturated bicyclic compounds. This aspect, which is now mainly of historical interest, will not be considered further here, particularly since it has been presented in great detail by *Fawcett*[4] in a survey of the literature published up to 1950.

Another aspect has proved to be interesting and important for the future[5, 6]. If the ring strain prevents the formation of a double bond at the bridgehead in the bicyclic structures *(1)* and *(2)*, it will certainly also do so in compounds with smaller rings, *e.g.* in the bicyclo[2.1.1]hexane system; however, this rule will not be absolutely valid for the higher homologs of *(1)* and *(2)*, since with a sufficiently large number of atoms in the ring it is possible to construct completely strain-free molecular models of bridgehead olefins. This raises the question how far the Bredt rule is valid for the higher homologs of *(1)* and *(2)*, or in other

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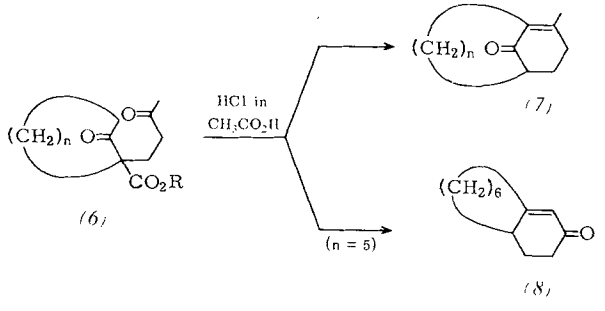
words, the ring size beyond which it is no longer valid. When considered in this way, the rule changes from a fact to a problem, and from an aid in the investigation of structures to a subject for investigation, whose current interest is shown by a number of very recent studies. It would admittedly be inappropriate to consider this problem in isolation. It forms part of the broader chemistry of strained ring systems, with which it is closely interwoven. The aim of the following discussion is to fit the Bredt rule into its place in this wider context.

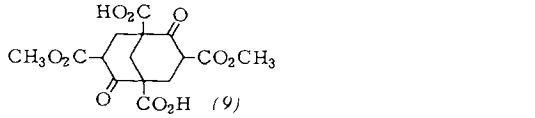
2. Isolable Bridgehead Olefins

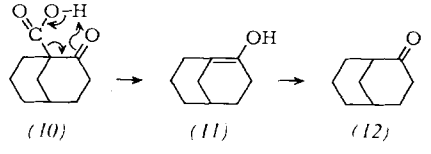
The range of validity of the Bredt rule, in the sense of our problem, can be defined only by negative evidence. The successful preparation of a bicyclo[*x.y.z*]alk-1-ene shows that the rule is not valid for this compound, though failure to prepare this compound does not necessarily indicate the validity of the rule. The information derivable from an experiment is thus crucially dependent on the appropriate choice of experimental conditions, particularly the "correct" synthetic pathway. A highly strained compound will be formed only if a sufficiently energy-rich precursor that reacts irreversibly and in only one direction is available, and its isolation will be successful only if no subsequent reactions occur.

The first attempts to establish a boundary were made in 1948/49 by *Prelog et al.*[7] in the intramolecular aldol condensation of the compounds *(6)*. The compounds *(7)* with a bridgehead double bond were formed smoothly from the homologs with $n \geq 5$; with $n=5$, *(8)* was formed in addition to *(7)* in an alternative reaction, and with $n<5$ *(7)* was no longer obtained.

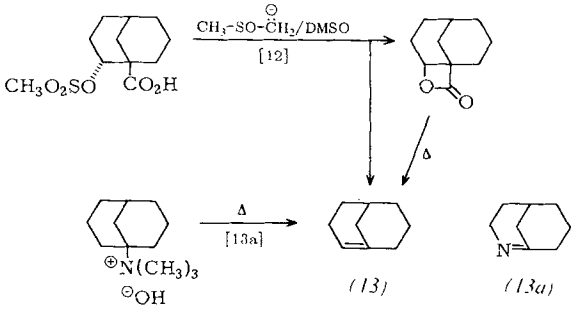


For purposes of comparison, it is useful to denote the sum $x+y+z$ of the numbers of bridge atoms in a bicyclo[*x.y.z*]alk-1-ene by *S*, as was done by *Fawcett*[4]. In the following discussion, moreover, the number for the bridge containing the bridgehead double bond will be indicated by a bar. The compound *(7)*, $n=5$, for which the Bredt rule is no longer valid according to *Prelog et al.*, is thus a [5.3̄.1] system with $S=9$. The ability of even smaller bicyclic structures with a bridgehead double bond, such as the [3̄.3.1] compound *(13)*, with $S=7$, to exist at least for a short time was suggested by the smooth decarboxylation of bicyclic β-keto acids such as *(9)*[8] and *(10)*[9].

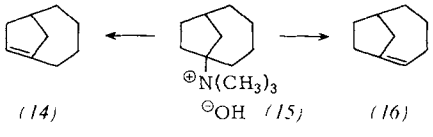




According to the current view on the decarboxylation mechanism of β-keto acids[10], this reaction should proceed *via* enols having the ring skeleton *(11)*. A similar conclusion can be drawn from the *triple* H/D exchange in the ketone *(12)* in basic media[11]. In 1967, the research groups of *Marshall*[12] and *Wiseman*[13a] succeeded in preparing the stable bicyclo[3.3.1]non-1-ene *(13)* by the three paths outlined below. The aza analog *(13a)* is now also known[14].



The isomeric [4.2̄.1] and [4̄.2.1] systems *(14)* and *(16)* were also synthesized shortly afterwards. Hofmann elimination in *(15)*, with kinetic product control, gave the (presumably) thermodynamically less stable *(14)* in higher yield than *(16)*[13b].



3. Relations between Structure and Ring Strain

The hydrocarbons *(13)*, *(14)*, and *(16)* at present mark the lower limit for stable bridgehead olefins. This admittedly does not mean that compounds having $S=7$ in general lie outside the range of validity of the Bredt rule, since the number of bridge atoms *S* gives only an incomplete picture of the ring strain. It can be used for predictions regarding strain and stability only when one is considering similar (homologous) bicyclic structures. Bridgehead olefins might even possibly be more stable than bicyclic systems with different structures and with a higher *S*. Another determining factor for a given *S* is the size of the individual bridges. The stability also depends on whether, for a fixed

ring skeleton, the bridgehead double bond is situated in a larger or in a smaller bridge. The following rules, which admittedly do not yet allow comparison in every case, can be deduced for bicyclic structures with the aid of models:

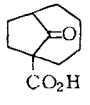
Rule A. For homologs with different S values, the ring strain varies inversely with S[4].

Rule B. For a given S, the ring strain varies inversely with the size of the larger of the two rings with respect to which the bridgehead double bond is *endocyclic*[13] (for explanations and reasons see Section 7).

Rule C. For a given bicyclic ring skeleton, the ring strain varies inversely with the size of the bridge containing the bridgehead double bond.

Rule C explains, for example, the greater stability of *(16)* in comparison with *(14)*. It follows from rules B and C, for example, that *(15)* does not give the least stable [4.2.1̄] system *(17)*, whose lower formation tendency is also reflected in the failure[15] to decarboxylate the β-keto acid *(18)*.

(17)



(18)

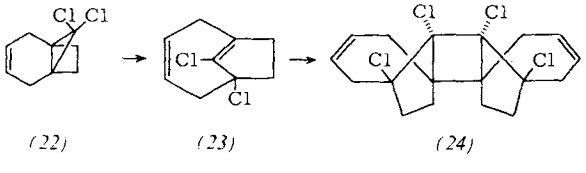
According to rule C, among the as yet unknown bicyclic structures *(19)* to *(21)*, *(19)* should be less stable than *(13)*, and *(21)* should be less stable than *(20)*. The investigation of these systems with $S=7$ should be interesting and important, since they presumably lie on the borderline between stable and unstable compounds as defined in Section 6.

(19)

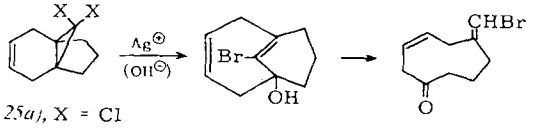
(20)

(21)

Initial reports of such investigations have appeared in very recent publications. Thus the [4.2.1̄] compound *(23)* is formed as a short-lived intermediate by cyclopropyl-allyl rearrangement of dichlorocyclopropane *(22)* at about 25 °C, as shown by the isolation of the head-to-head dimer *(24)* whose structure has been elucidated by X-ray methods (mirror symmetry)[46a]. The ring strain in *(23)* is estimated as 20—22 kcal/mol. The dichloride *(25a)*, a higher homolog of *(22)*, is thermally stable. However, the corresponding dibromide *(25b)* (and likewise also the dihydro derivative)



(22) *(23)* *(24)*

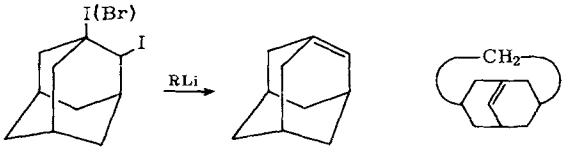


(25a), X = Cl
(25b), X = Br

(26) *(27)*

undergoes silver-salt catalyzed skeletal rearrangement to the cyclononene compound *(27)*, the [4.3.1̄] system *(26)* being a suspected intermediate[46b].

We encounter a particularly interesting bridgehead olefin in adamantene *(29)* which turns out to be a derivative of the [3.3.1̄] system *(19)* when drawn in the distorted fashion chosen for formula *(30)*, but with an even higher ring strain owing to the additional methylene group. Its intermediacy in the dehalogenation of 1,2-diiodo (and 1-bromo-2-iodo-)adamantane *(28)* by organolithium compounds is apparent from the almost quantitative formation of a hydrocarbon $C_{20}H_{28}$[47], which is presumably a head-to-tail dimer of *(29)*[47a]. *(29)* is assumed to have a "double bond" with completely decoupled π electrons[47b].



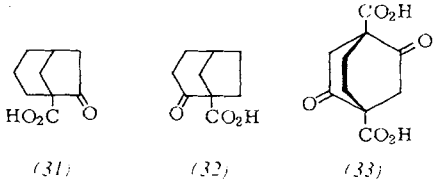
(28) *(29)* *(30)*

Thus no isolable [$x.y.1̄$] compounds have so far been obtained with $S=7$; the bridgehead olefins of this structure under current investigation belong to the unstable intermediates to be discussed below.

4. Unstable Compounds with $S<7$

According to the current view, bridgehead olefins with $S<7$ are capable of existing, but are unstable. Our as yet very incomplete knowledge is based on the circumstantial evidence that is usual for short-lived intermediates, and is subject to the uncertainties associated with this method.

This is true *e.g.* for the above-mentioned decarboxylation of β-keto acids with carboxyl groups attached to the bridgehead carbon atom. The fact that decarboxylations occur with difficulty if at all in systems with $S \leqslant 6$[16-19] can be safely interpreted as resistance to the formation of the corresponding ring-strained enols. On the other hand, it is very doubtful whether the normal decarboxylation mechanism *via* enols [see formulas *(10)* and *(11)*] is followed under forcing conditions, as in the thermolyses of the β-keto acids *(31)*, *(32)*[18] and *(33)*[19] between 260 and 320 °C.

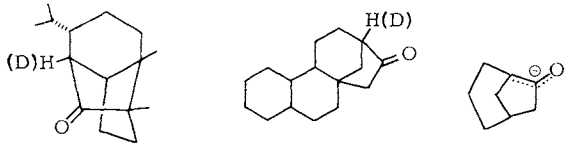


(31) *(32)* *(33)*

A variant has been proposed[18] (and criticized[13a, 20]), in which the bridgehead atom retains its sp^3 hybridization in the course of the elimination of CO_2. According to *Buchanan et al.*[20], the decarboxylation of optically active *(33)*, contrary to expectation, proceeds with complete race-

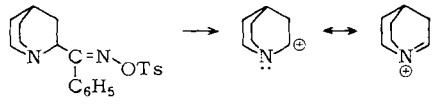
mization. It could therefore involve an initial ring cleavage, followed by the normal decarboxylation and a recyclization. It is significant that the monocarboxylic acid formed from *(33)* is not decarboxylated further[20].

The decarboxylation of small bicyclic β-keto acids obviously does not allow reliable deductions concerning the existence or non-existence of ring-strained bridgehead olefins, owing to its unconfirmed mechanistic premises. Nevertheless, the recently accomplished base-catalyzed H/D exchange at the bridgeheads of the ketones *(34)*[48a] and *(35)*[48b] that are adjacent to the carbonyl groups provides some indication of the existence of enolates of type *(36)*, however short-lived they may be.



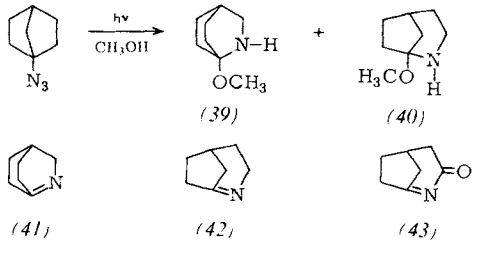
(34) *(35)* *(36)*

Azabicycloolefins with $S=6$ have been variously postulated as intermediates. Thus the thermolysis of *O*-tosyl-2-quinuclidinyl phenyl ketoxime proceeds partly as a fragmentation *via* the carbenium ion *(38a)* and is faster than that of the homomorphous alicyclic compound, which decomposes exclusively by Beckmann rearrangement. The greater formation tendency of *(38a)* can be explained by resonance stabilization involving the bridgehead-immonium mesomeric structure *(38b)*[21].



(37) *(38a)* *(38b)*

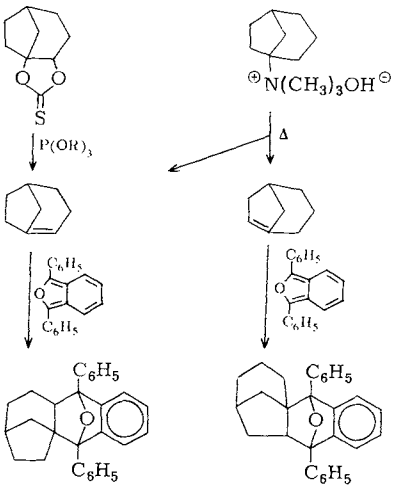
The azabicyclic compounds *(39)* and *(40)* formed in roughly equal amounts on photolysis of 1-azidonorbornane in methanol could be derived from the primary ring-expansion products *(41)* and *(42)* by addition of methanol. However, the authors[22a] favor a synchronous process that avoids these energy-rich intermediates. The *N*-protonated *(42)* is nevertheless postulated as an intermediate in the reduction of *(40)* with $LiAlH_4$ [to *(40)* with H instead of OCH_3][22a]. The unsaturated lactam *(43)* is a plausible intermediate in the oxidation of the corresponding saturated lactam with lead tetraacetate[22b].



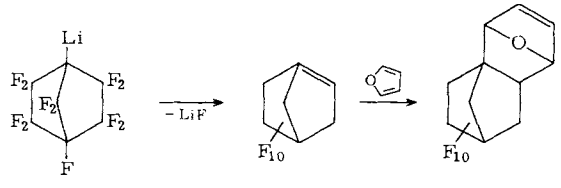
(39) *(40)*

(41) *(42)* *(43)*

Evidence has recently also been obtained for the intermediacy of bicyclo[3.2.1]oct-1-ene[13c]: thermolysis of the thiocarbonate 2,4-dioxatricyclo[6.2.1.0^{1,5}]undecane-3-thione with trialkyl phosphite in the presence of 1,3-diphenylisobenzofuran yields 62% of a mixture whose spectral data are compatible with the structure of the expected Diels-Alder adduct (mixture of stereoisomers). Hofmann elimination with the structurally analogous quaternary ammonium hydroxide gives 0.3% of a product which could also contain the adduct of the [3.2̄.1]bicycloolefin.

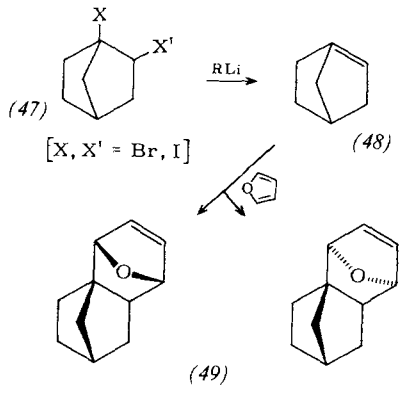


For these reasons and on the basis of the following observations, therefore, it may be assumed that bicyclic systems with $S=6$ and a double bond at the bridgehead can exist, though there is as yet no satisfactory experimental proof. It should be stressed that conclusive proof of this would not be contrary to the Bredt rule in its original version, which was formulated for systems with $S=5$. It is interesting to note, however, that two "forbidden" 1-norbornenes ($S=5$) have recently been detected as short-lived intermediates. In 1965, *Tatlow et al.* observed the elimination of LiF from 1-lithioperfluoronorbornane *(44)* to give perfluorinated 1-norbornene *(45)*, which was characterized mainly by its diene reaction with furan to form the two possible stereoisomers of the cycloadduct *(46)*[23a]. If the halogen at the bridgehead of *(44)* is replaced by H, however, the β elimination does not take place[23b]. Because of this surprising substituent effect, one cannot deduce the existence of the unsubstituted compound *(48)* from that of *(45)*. The existence of *(48)* was demonstrated in 1971 by *Keese* and *E.-P. Krebs*[24]: Dehalogenation of the vicinal dihalides *(47)* with butyllithium in the presence of furan results in the formation of the cycloadduct *(49)*. The 1-norbornene intermediate *(48)* is confirmed by the discovery that the two stereoisomers of *(49)* are always formed in a ratio of 1:4, regardless of the nature of the halogen and of the organometallic agent.

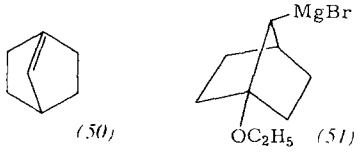


(44) *(45)* *(46)*

There is so far no evidence of the existence of the isomeric norbornene *(50)*. Its relatively (according to rules B and C) and absolutely low formation tendency is indicated on the one hand by the apparently exclusive formation

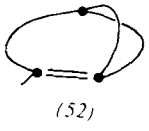


of *(45)* from *(44)* and on the other by the unusual thermal stability of the Grignard compound *(51)* (no β elimination at 80 °C)[25].



5. Causes of the Ring Strain

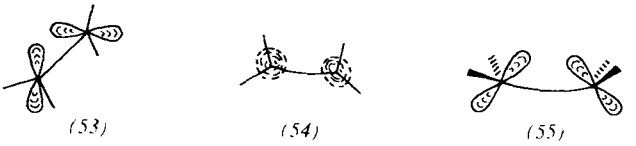
The instability of the bicyclic systems to which the Bredt rule is applicable is a result of the increased ring strain in relation to saturated compounds having the same structure, as mentioned earlier. The additional strain is due partly to the widening of tetrahedral angles to 120°, and mainly to the fact that a double bond does not exhibit the free rotation of σ bonds. The dihedral angles formed by the single bonds from the bridgehead atom with the valences from the other atom of the double bond are therefore no longer unimportant. The dihedral angles of 0° and 180° in the planar olefins cannot be achieved at bridgeheads of small bicyclic systems, since three of the four bonds from the ends of the double bond, as parts of the bicyclic system, curve away in the same direction, *i.e.* toward the other bridgehead [see formula *(52)*]. The two olefinic carbon atoms cannot therefore achieve the usual coplanar arrangement with the four atoms bonded to them, nor can they form the normal bond angles of 120°. The reasons for the ring strain are therefore as follows:


(52)

1. The most important and most characteristic reason is the twisting of the π bond about the axis joining the two olefinic carbon atoms[7].

This is a consequence of the fact that the four bonding partners of the olefinic carbon atoms cannot lie in the same plane, and optimum overlap of the two p orbitals is therefore prevented. The extreme case, with a twisting angle of 90°, would be a biradical or *C*-ylide [formula *(53)*].

2. Planar [formula *(54)*] and nonplanar [formula *(55)*] deformations of the σ bonds emerging from the unsaturated


(53) (54) (55)

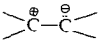
centers. These deformations combine to give a resultant that also influences the degree of overlap of the two p orbitals.

Little is known at present about the effects of these deformation forces on the nature of the "double bond". The distortion of the π bond is presumably accompanied by a change in hybridization, with admixture of s components into the p orbitals and an increase in the p character of the σ bonds. For *trans*-cyclooctene, whose relation to bridgehead alkenes will be discussed in Section 7, the configuration shown in formula *(56)*, with the bonds bent downwards and the orbital lobes on both carbon atoms extended in the opposite direction, has been proposed[26]. In bridgehead alkenes with non-equivalent olefinic carbon atoms, this change of hybridization should be greater for the bridgehead atom, which is more exposed to the shearing forces.

(56) (57)

According to preliminary model calculations by *Keese* and *Krebs*, the configuration shown in *(57)*, with a roughly sp^3-hybridized bridgehead atom and a p orbital on the neighboring atom, is in fact energetically more favorable than *(56)* for 1-norbornene *(48)*. Its π-bond order is only about half of that of ethylene, and it carries an excess charge on the bridgehead atom[24b].

The question arises whether the extreme case is not more adequately represented by a dipolar (*C*-ylide) structure



than by a diradical. No confirmatory experimental evidence has yet been obtained for this assumption. In polar additions to bicyclo[3.3.1]non-1-ene *(13)*, the nucleophile, contrary to the above model and in agreement with the Markownikoff rule, always adds to the bridgehead atom[12,13a]; however, this compound is much less strained, and is therefore possibly atypical. The spontaneous cyclodimerizations of unstable bridgehead olefins could provide more reliable information: assuming comparable steric conditions, head-to-tail cycloaddition should take precedence over the head-to-head process. However, the few results obtained so far indicate occurrence of both types.

6. Bredt Compounds

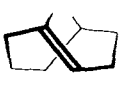
There are no empirical parameters available at present for the quantitative correlation of structural effects and ring strain. The Bredt rule is thus a qualitative statement with fluid boundaries. It would be unreasonable (and it

is not usual in the literature) to regard it in its original version (Section 1) as a strict prohibition of existence for certain compounds. Exceptions were mentioned in Section 5, and future investigations will undoubtedly show that other "forbidden" bicyclic systems can exist, so that the Bredt rule would ultimately become meaningless, despite its inherent value. The objection that the "forbidden" compounds do not possess a "true" double bond, but are biradicals or betaines, would be too sophistic an apology. It seems much better to interpret the Bredt rule as characterizing an unstable rather than a non-existent class of bicyclic compounds. It is then possible and meaningful to refer to the bicyclic systems to which it is applicable as "Bredt compounds" (see also Scheme 1 in Section 10) and to define them as follows: "Bredt compounds are bicyclic (and polycyclic) systems (alicycles and heterocycles) that, in addition to a strained σ-bond skeleton, have a twisted π bond at a bridgehead, and *purely* because of this ring strain, in contrast with compounds having the same structure but without this π bond, are unstable at room temperature."

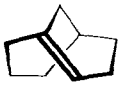
7. Comparison with Strained *trans*-Cycloalkenes

The above definition of Bredt compounds is based primarily on ring-strain rather than structural criteria. It is thus more comprehensive than the original Bredt rule, even in its extended form given in the introduction. To illustrate the consequences, let us consider some classes of ring-unsaturated compounds whose unstable members, in part, are not Bredt compounds by definition, and in part have until now been traditionally regarded as not being subject to the Bredt rule.

The relationship of the Bredt bicyclic systems with the *trans*-cycloalkenes, which was recognized as early as 1933 by *Ebel*[6], is particularly striking. According to *Allinger*[28a], the ring strain in *trans*-cyclooctene *(58)*, the smallest stable member[27], is due to the same deformation forces that occur in Bredt compounds according to Section 5, as can be seen from molecular models. In fact, bicyclo[3.3.1]non-1-ene *(13)* (Section 2), the smallest stable bridgehead olefin, may be regarded as a bridged *trans*-cyclooctene, and can be constructed from the latter in models without much additional strain [formulas *(58)* and *(59)*][13a]. According to thermochemical data, *(13)* has a ring strain of 12 kcal/mol, as compared with 9.2 kcal/mol in *trans*-cyclooctene[29]. The calculated heat of hydrogenation of *(13)* is 12.85 kcal/mol less, *i.e.* its ring strain is greater by this amount, than that of the Δ^2 isomer[28b]. The instability of bicycloolefins smaller than *(13)* is paralleled by the instability of *trans*-cycloheptene[30], whose calculated ring strain is about 10 kcal/mol higher than that of *trans*-cyclooctene[28b].



(58)

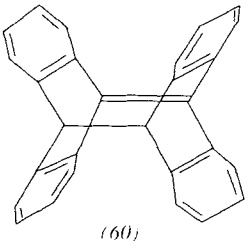


(59) [≡ *(13)*]

A double bond at the bridgehead of a bicyclic system is always exocyclic with respect to one of the three rings and endocyclic with respect to the other two. According to *Wiseman*[13], the number of atoms in the larger of the two rings with the endocyclic double bond provides information about the relative stability of the bicycloalkene (rule B, Section 3). This explains *e.g.* the greater stability of the [$\bar{3}$.3.1] and [$\bar{4}$.2.1] systems *(13)* and *(16)* in comparison with the [3.3.$\bar{1}$] and [4.2.$\bar{1}$] isomers *(19)* and *(17)*, since the largest ring with an endocyclic double bond is cyclooctene in the first two compounds as opposed to cyclohexene and cycloheptene, respectively, in the other two. The applicability of this rule is admittedly limited, since it does not allow comparison of isomers such as *(14)* and *(16)* or *(20)* and *(21)* ([$\bar{x}$.*y*.*z*] and [*x*.$\bar{y}$.*z*] systems in general) that differ only in the position of the double bond in the largest unsaturated ring. In this case rule C provides supplementary information.

8. Systems Containing a Zero Bridge

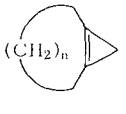
[$\bar{x}$.*y*.0] systems, *i.e.* bicyclic systems with a zero bridge, were always tacitly or expressly[4] excluded from the problem of the Bredt rule in the past. This restriction does not exist in our definition of Bredt compounds. If an unstable [$\bar{x}$.*y*.0] system exhibits the strain characteristics mentioned, it can be classified as a Bredt compound; otherwise it cannot. To establish a limit, let us consider some strained bicyclic systems; in order to determine the causes of their ring strain, we shall again use their imaginary derivation from unsaturated monocycles.



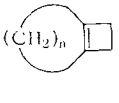
(60)

A revealing limiting case from the standpoint of the last section is the strained hydrocarbon *(60)*, which was prepared by *Weinshenker* and *Greene* in 1968[31] (its 5-chloro derivative was known even earlier as an intermediate[32]). It may be regarded as a doubly bridged *trans*-cyclooctene, but on symmetry grounds, only non-planar deformation forces act on its double bond (see Section 5); it thus lacks the twisting of the double bond that is typical of Bredt compounds. A significant feature is the direct linkage of two bridgeheads by a double bond.

(61)



(62)

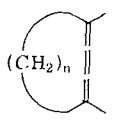


(63)

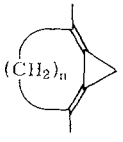
The same is true of 1,2-bridged cyclopropenes *(62)* and cyclobutenes *(63)*, which can be derived from the corresponding cycloalkynes *(61)* by expansion of the π bond, which lies *in* the plane of the ring, to a three-membered or four-membered ring. The smallest stable cycloalkyne

is the sterically shielded 3,3,7,7-tetramethylcycloheptyne [skeleton: *(61)*, $n=5$][33]; the cyclopropenes *(62)* become unstable on transition from $n=5$ to $n=4$[34], and the cyclobutenes *(63)* on transition from $n=3$[35] to $n=2$[36].

In the cyclobutatrienes *(64)*, with 1,2,3-cyclodecatriene [*(64)*, $n=6$] as the smallest stable compound[37], expansion of the π bond, which is situated *in* the plane of the ring, leads to the bridged bismethylenecyclopropanes *(65)*, which should be isolable with $n=5$ or even 4 because of the associated bending of the central σ bond.



(64)

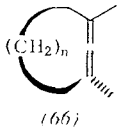


(65)

In small-ring cycloalkynes and cyclobutatrienes, the π bonds, whose orbitals lie in the plane of the ring, are subject to planar deformation forces, but not to twisting strains. The same is true of the bicyclic systems *(62)*, *(63)*, and *(65)*, as is confirmed by molecular models. Unstable bicyclic systems with a zero bridge are thus not Bredt compounds if the double bond is also the zero bridge or if the same bridge contains another double bond at the other bridgehead.

The situation is different in bicyclic systems that can be thought of as derived from cycloallenes *(66)*. The smallest compound of this type that is stable at room temperature is 1,2-cyclononadiene [*(66)*, $n=6$][38]; lower homologs with $n=3$ to 5 are unstable[39], but the homolog with $n=5$ has been detected directly by spectroscopy at low temperatures[40].

Cycloallenes present another, formerly overlooked analogy between the ring strain of unstable monocyclic systems and that of Bredt compounds. Short methylene bridges cause not only planar and non-planar deformations of the two double bonds, but also twisting of the π bonds, since they distort the end valences of the allene from the natural dihedral angle of 90° toward a coplanar arrangement. If one π bond of the allene is expanded to a three-membered ring, we obtain a bridged methylenecyclopropane *(67)*. The same forces typical of Bredt compounds that act in the cycloallene *(66)* also act in the methylenecyclopropane, but the ring strain for a given ring size is less, since the three linearly arranged carbon atoms in *(66)* now form an angle of about 150°, and their end valences form a dihedral angle of less than 90°.



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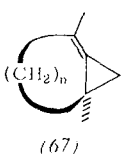
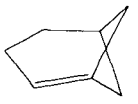
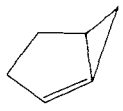


(67)

This relationship with "classical" Bredt compounds can also be demonstrated as follows. If a carbon atom bonded to two bridgeheads is cut out of bicyclo[3.1.1]hept-1-ene *(68)*, which certainly is a Bredt compound, we obtain the compound *(69)*, which is identical with *(67)*, for $n=2$. This should have a ring strain roughly comparable with that of *(68)*, but the twisting strain is slightly reduced in favor of the deformation forces (see Section 5). Thus



(68)

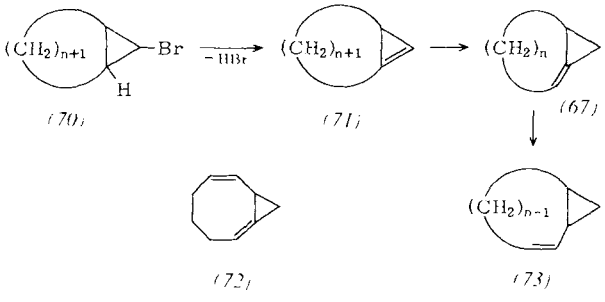


(69)

if an $[\bar{x}.1.1]$ or $[x.\bar{1}.1]$ system is a Bredt compound, the $[\bar{x}.1.0]$ or $[x.\bar{1}.0]$ system with one carbon atom less may be assumed to be a Bredt compound too. We note as a selection rule, however, that a one-carbon bridge containing a double bond cannot be removed, since this would give a bicyclic system with a double bond between the two bridgeheads.

9. Bridged Methylenecyclopropanes as a Test Case for the Bredt Rule

According to the above argument, bridged methylenecyclopropanes *(67)* can be used as a basis for statements regarding the range of validity of the Bredt rule. Compounds *(67)* with $n\geq 6$ are obtainable by carbene additions to cycloallenes *(66)*, and are stable[37]. According to *Gardner et al.*[41a], lower homologs are formed on dehydrobromination of bridged bromocyclopropanes *(70)* with strong bases.

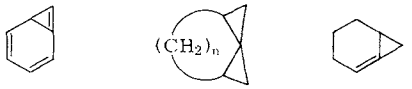


(70) *(71)* *(67)* *(72)* *(73)*

However, only bicyclo[6.1.0]non-1-ene [*(67)*, $n=5$] can actually be isolated; the didehydro derivative *(72)* can be prepared analogously by double dehydrochlorination of 9,9-dichlorobicyclo[6.1.0]nonane[41b]. As was mentioned earlier, these two compounds may be compared with bicyclo[6.1.1]dec-1-ene, $S=8$, and are therefore stable as expected. The bicycles *(67)* with $n\leq 5$ that are of interest to our discussion, on the other hand, cannot be isolated in basic media, because of their rearrangement to the less strained Δ^2 isomers *(73)*[41a]; more highly unsaturated derivatives undergo further additions and skeletal rearrangements[41b,42]. Since the formation conditions favor isomerizations, no conclusions can be drawn from these results concerning the thermal stability of the bridged methylenecyclopropanes *(67)* with $n\leq 5$. The same is true for the bridged cyclopropenes *(71)*, whose unsaturated member *(74)* was postulated as an intermediate in the phenylcarbene rearrangement[43].

Literature data allow the following assessment. The bridged methylenecyclopropanes *(67)* are formally links between

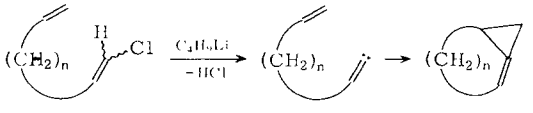
the cycloallenes *(66)* and the tricyclo[x.1.0.0^{1,3}]alkenes *(75)*. The former are stable from the nine-membered ring on (see above), and the latter from the five-membered ring on [*(75)*, $n=2$][43]. It should therefore also be possible



(74) *(75)* *(76)*

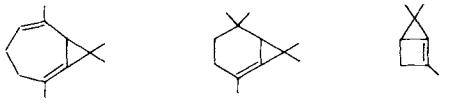
to isolate the compound *(67)* with a seven-membered ring ($n=4$). *(69)*, which contains two bridge atoms less than *(67)*, $n=4$, is clearly unstable according to the above arguments, and the link *(76)* is thus an interesting test case.

Starting with suitably substituted chloroolefins of the type *(77)*, we checked these predictions for the intramolecular cyclopropanation of unsaturated carbenes *(78)* as represented by the following scheme, which, having a high driving force, proceeds under mild conditions and without subsequent isomerization[44].



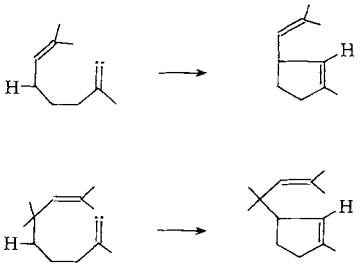
(77) *(78)* *(67)*

In this way a (substituted[*]) chloroolefin *(77)* with $n=4$ gave a stable hydrocarbon, to which the constitution *(79)* was assigned[44a]. From a lower homolog with $n=3$, it was possible to obtain the compound *(80)*, whose double bond at the bridgehead has been confirmed[44b]. The compound *(80)* decomposes at room temperature with a half-life of about 70 hours, and can thus be classified as a Bredt compound. The next lower homolog *(82)*, as expected, could not be isolated. Its transient existence has been deduced from the formation of dimeric hydrocarbons $C_{18}H_{28}$: The pentacyclic system *(83)*, whose structure has been established by X-ray analysis[44f], is the main product $\leq -50\,^{\circ}C$ and obviously results from a head-to-head *exo* addition of two molecules of *(82)*. The major

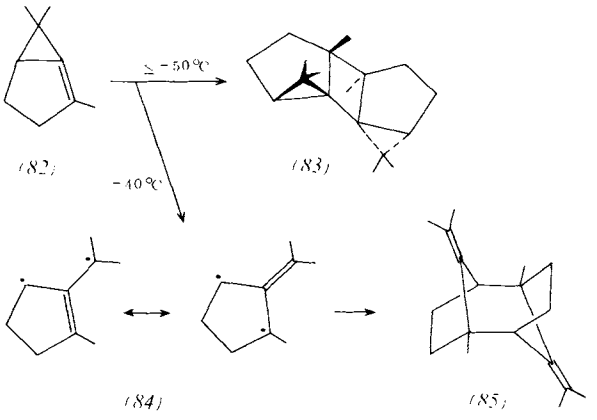


(79) *(80)* *(81)*

[*] The methyl groups prevent elimination to form an acetylene and facilitate the cyclopropanation. The additional double bond in *(67)* prevents intramolecular CH insertion of the intermediate carbenoid, which always occurs readily if the formation of a cyclopentene is possible [44a, 44e]:



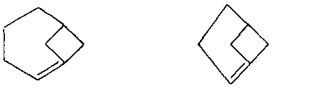
product at $-40\,^{\circ}C$ is the tricyclic compound *(85)* (the spectroscopic data are also in accord with a structure having two methyl groups at *neighboring* bridgehead atoms), which is probably formed *via* the trimethylenemethane intermediate *(84)*[44c].



(82) *(83)* *(84)* *(85)*

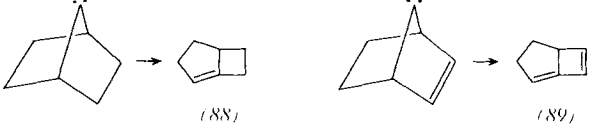
The limits of the cyclization *(78)*→*(67)* are reached with the trimethyl derivative of *(78)* with $n=1$, which reacts *inter*molecularly instead of undergoing the intramolecular reaction to form the enormously strained bicyclo[2.1.0]-pent-1-ene *(81)* ("housene")[44d].

On the basis of the above results and arguments, it can be predicted for the homologous series of bicyclo[x.1.1]alk-1-enes that *(86)* ($S=6$) and *(87)* ($S=5$) are compounds that can exist with moderate and short lifetimes respectively; the higher homolog *(20)* ($S=7$) might be stable at room temperature.



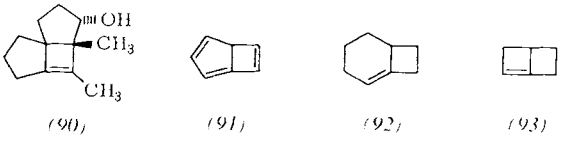
(86) *(87)*[≡*(68)*]

[$\bar{n}$.2.0] and [n.$\bar{2}$.0] systems with sufficiently small n are also Bredt compounds. However, they are more flexible than bridged methylenecyclopropanes *(67)* and cyclopropenes *(71)* having the same number of bridge atoms. The recent literature contains reports on the isolation of *(88)* and *(89)* from carbene isomerizations[45a], the



(88) *(89)*

synthesis of *(90)* as a derivative of a photoisomerization product[45b], and the intermediate occurrence of the compound *(91)*[45c]; the higher homolog *(92)* is also

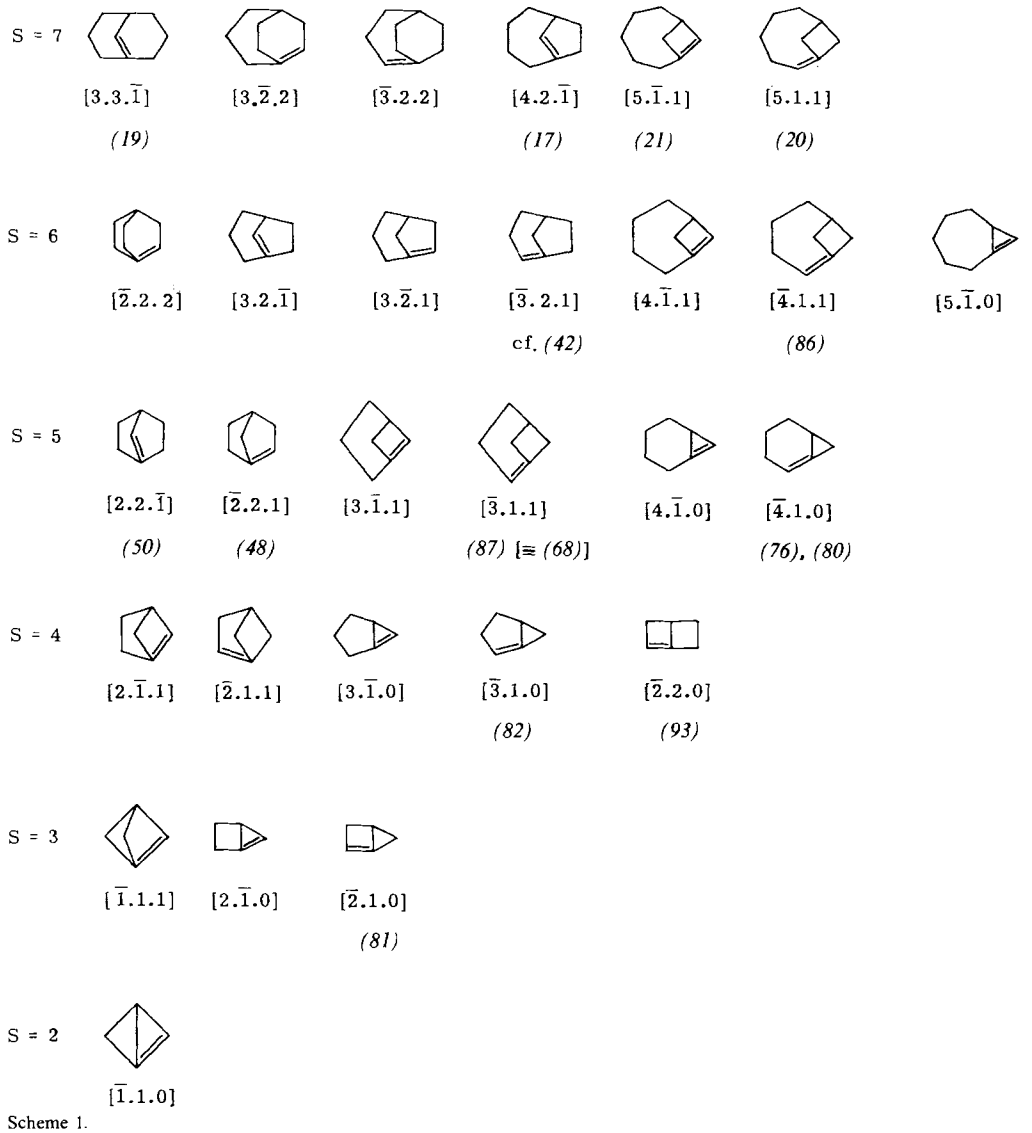


(90) *(91)* *(92)* *(93)*

known[45d]. The boundary between stable and unstable compounds is evidently crossed only with [2̄.2.0] systems *(93)*.

10. Outlook

Scheme 1, to which one could add a long series of heterocyclic and polycyclic analogs, shows 28 bicycles containing a bridgehead double bond and with $S \leqslant 7$, which may nowadays be assumed to be Bredt compounds, or for which at least the reverse has not yet been proved. Insofar as any conclusion can be drawn from rules A to C, these compounds are arranged from top to bottom and from right to left in order of increasing ring strain; the majority have not yet been investigated. One could naturally argue about whether the hypothetical bicyclo[1.1.0]but-1-ene, which stands at the end of the series, should really be classified as a Bredt compound, since its immense ring strain must be due much more to deformation of the σ skeleton than to twisting strains on the unsaturated centers. One can see here the entanglement of our problem with other aspects of the chemistry of ring-strained hydrocarbons. However, one cannot deny the heuristic value of the Bredt rule as a guideline and stimulus for synthetic and mechanistic studies.



Scheme 1.

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Anomalies in the Structural Chemistry of Silicon

By Hans Bürger[*]

In contrast to carbon, silicon fails to form multiple bonds that are stable at room temperature. Consequently molecules in which silicon exhibits coordination numbers (CN) of 1, 2, and 3 may only be obtained at very high or low temperatures. Under these conditions their structural features, including multiple bonds, resemble those of carbon. On the other hand, silicon is capable of forming various hexacoordinated compounds making use of its d orbitals. Nitrogen and oxygen bonded to silicon develop an unusual stereochemistry: planar nitrogen, nearly or completely linear oxygen, and considerable shortening of SiN, SiO, and SiF bonds are specific examples. $N(SiR_3)_2$ and CH_2SiR_3 ligands permit stabilization of unusually low CNs of many metals and give rise to amino and alkyl derivatives of unexpectedly high stability due to the particular electronic, steric, and kinetic effects of the R_3Si group.

1. Introduction

The rapid increase in the number of new silicon compounds was for a long period not adequately accompanied by structural investigations. The limited structural data available 10 to 20 years ago suggested in some cases close analogies with carbon but in other cases significant specific behavior of silicon was indicated, for which a bonding theory different from that for carbon was adopted.

Research in the fields of reaction mechanisms (*L. H. Sommer*), of physical chemistry (*e.g.* photoelectron spectroscopy) and of molecular structure determinations has increasingly extended our knowledge of the bonding and structural characteristics of silicon. In particular the renaissance of electron diffraction during the last few years has enabled an almost comprehen ive series of structural determinations of suitably volatile silicon compounds; many of these investigations were performed by *G. M. Sheldrick* and *A. G. Robiette*.

The present widened physico-chemical basis of silicon chemistry[1] and the extent of available structural information nowadays permit and justify selection of those features specific to silicon which distinguish it from carbon. These are presented in the following review which, however, is not intended to be exhaustive, attention being focused primarily on silicon's "exotic" CNs 1, 2, 3, 5, and 6 which have not previously been given such consideration[1-3].

Apart from the structural anomalies to be discussed silicon exhibits of course a vast range of normal structures more closely resembling those of carbon, but, as with the chemical properties, predictable differences occur due to the greater atomic radius and the lower electronegativity. They are reflected, *e.g.*, in the steric requirements of the R_3Si group, its mobility with respect to 1,2; 1,4; O,N; and CN,NC migrations, and other fluxional behavior.

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2. Silicon with CN 1

Di- and triatomic molecules and ions containing a Si atom involved in only one bond of variable bond order are remarkably well known from microwave, matrix IR, and electronic absorption and emission spectra at different resolutions. The methods of investigation applied must take into account the short lifetime and the narrow range of stability at unusual temperatures. Astrochemistry has shown that these conditions frequently prevail in extraterrestrial space, the radiation of many stars arising from emission of the electronic spectra of silicon derivatives such as SiF or SiCC. The studies leading to the following results have been considerably stimulated by astrochemistry.

It is of course true that no molecule such as CO, which is stable at room temperature, is known in silicon chemistry. The analogous SiO polymerizes at a few °K forming $(SiO)_2$, $(SiO)_3$[4], and species of higher degrees of polymerization, fragmentation into monomeric SiO occurring upon heating to 1500 °K.

In view of this difference between CO and SiO and the opposite sign of the dipole moment in chalcogenides of carbon and silicon (due to the lower electronegativity of Si; Table 1) the electronic structures and (relative) molecular parameters of species with CN 1 differ less than one might have expected[5].

Table 1. Dipole moments [D] of chalcogenides $E^{IV}E^{VI}$; from ref. [6].

E^{IV} =	C	Si	Ge
E^{VI} = O	−0.112(5)	3.0982(10) [a]	3.2824(10)
S	−1.958(5)	1.73(6)	2.00(6)
Se		1.1(2)	1.648(50)
Te			1.06(7)

[a] Associated with the vibrational level v = 0 of $^{28}Si^{16}O$; v = 1: 3.1178, v = 2: 3.1372, v = 3: 3.1574 D.

The approximate ionization potentials listed in Table 2 suggest a separation of p from s electrons for both C and Si of 7—10 eV. Consequently considerable interaction

Table 2. Ionization potentials [eV] of valence electrons.

	C $^3Ps^2p^2$ [a]	C sp^3 [b]	Si $^3Ps^2p^2$	Si sp^3 [b]	Si s^2pd [c]
s	19.4	20.0	14.7	16.0	18.2
p	10.7	10.0	8.1	7.5	11.5
d					1.8_5

[a] Average ionization potentials from ref. [7];
[b] according to Hartree-Fock, quoted in ref. [8];
[c] according to Hartree-Fock; quoted in ref. [1].

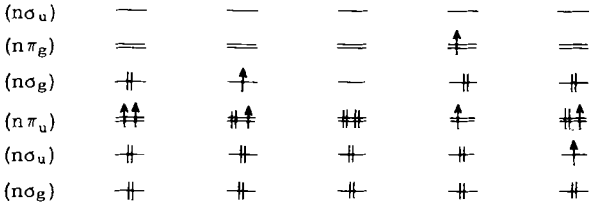
is expected to occur between molecular orbitals of appropriate symmetry to which ns and np of Si (and C) have contributed. This favors the following order of molecular orbitals

$$\ldots(n\sigma_g)(n\sigma_u)(n\pi_u)\ n\sigma_g)(n\pi_g)(n\sigma_u)$$

(Scheme 1) for C_2, Si_2, CO, and SiO, the energies of $(n\pi_u)$ and $(n\sigma_g)$ however being quite similar. Of these orbitals $(n\pi_u)$ is strongly bonding while both $(n\sigma_u)$ and $(n\sigma_g)$ may vary between weakly bonding and antibonding in character. In consequence such differences cause ground and excited state electronic structures which differ for C and Si.

C_2 and Si_2

While C_2 has a singlet $X^1\Sigma_g^+$ ground state[*], both this state and the triplet state $^3\Pi_u$ of approximately the same energy are excited states for Si_2 which has a $^3\Sigma_g^-$ ground state[8,9]. Comparison of the $^3\Pi_u$ and $^3\Pi_g$ molecular parameters (*a* and *d* for C_2, *D*, and *L* for Si_2; Scheme 1) reveals an increase in bond order for C_2, but a decrease for Si_2. This is qualitatively suggested assuming a stronger antibonding character of the $(n\sigma_g)$ MO for Si_2 than for C_2. A similar difference is observed for C=C=C/Si=C=C[10] and likewise for CN and SiN.

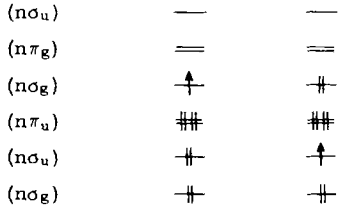


	$^3\Sigma_g^-$	$^3\Pi_u$	$^1\Sigma_g^+$	$^3\Sigma_u^-$	$^3\Pi_g$
C_2	*b*	*a*	*X*	—	*d*
T_e [cm^{-1}]	6537	716	±0	—	20023
ω_e [cm^{-1}]	1470	1641	1856	—	1788
r_e [Å]	1.369	1.312	1.242	—	1.266
Si_2	*X*	*D*	—	*H*	*L*
T_e [cm^{-1}]	±0	a	—	24075	a + 28059
ω_e [cm^{-1}]	511	548	—	271	—
r_e [Å]	2.246	2.155	—	2.663	2.255

Scheme 1. Electronic structures of C_2 and Si_2.

A $X^2\Sigma^+$ ground state (Scheme 2) is common to both CN and SiN[5,11]. On going to the second excited state $B^2\Sigma^+$ ($A^2\Pi_i$ has not yet been observed for SiN), which requires 3.1 ± 0.1 eV in both cases, shortening of the CN bond, but lengthening and weakening of the SiN bond occur. An approximate bond order of 2.5 may be assigned to both ground states.

The aim of this arbitrary selection is to demonstrate that the molecular parameters are fairly similar in corresponding derivatives of monovalent carbon and silicon. Except for CO and its derivatives such as isonitriles, instability



	$^2\Sigma^+$	$^2\Sigma^+$
CN	*X*	*B*
T_e [cm^{-1}]	±0	25752
ω_e [cm^{-1}]	2069	2164
r_e [Å]	1.172	1.151
SiN	*X*	*B*
T_e [cm^{-1}]	±0	24299
ω_e [cm^{-1}]	1152	1031
r_e [Å]	1.572	1.580

Scheme 2. Electronic structures of CN and SiN.

at room temperature is common to all molecules of this group, in which the anomalous behavior of silicon is least pronounced.

[*] Regarding the use of the symbols employed here and in the following see IUPAC: Manual of Symbols and Terminology for Physicochemical Quantities and Units. Butterworths, London 1970, p. 29.

Atomic spectroscopy

The letter-symbols indicating quantum states are:

$L,l = 0$: S, s	$L,l = 4$: G, g	$L,l = 8$: L, l
$= 1$: P, p	$= 5$: H, h	$= 9$: M, m
$= 2$: D, d	$= 6$: I, i	$= 10$: N, n
$= 3$: F, f	$= 7$: K, k	$= 11$: O, o

A right-hand subscript indicates the total angular momentum quantum number *J* or *j*. A left-hand superscript indicates the spin multiplicity $2S+1$.

Examples:

$^2P_{3/2}$—state ($J = 3/2$, multiplicity 2)
$P_{3/2}$—electron ($j = 3/2$)

An atomic electron configuration is indicated symbolically by:

$$(nl)^\kappa(n'l')^{\kappa'}\ldots$$

Instead of $l=0, 1, 2, 3, \ldots$ one uses the quantum state symbols s, p, d, f, ...
Example: the atomic configuration: $(1s)^2(2s)^2(2p)^3$

Molecular spectroscopy

The letter symbols indicating molecular electronic quantum states are in the case of *linear molecules:*

$\Lambda,\lambda = 0$: Σ, σ
$= 1$: Π, π
$= 2$: Δ, δ

and for *non-linear molecules:*

A, a; B, b; E, e; *etc.*

3. Silicon with CN 2

Structural differences are more developed in compounds of C and Si with CN 2. While SiO_2 resembles SiO and HNSi in failing to form a monomer stable at room temperature, singlet-SiF_2 is in contrast thermally more stable than singlet-CF_2. The former polymerizes in the gas phase at room temperature and low pressure with a half-life of minutes, whereas the latter has a half-life of approximately 1 s at 1 torr and room temperature, which is nevertheless remarkable for a carbene. The ease of formation and stability of silylenes has promoted extensive development of their chemistry which shows many similarities to carbene chemistry[12].

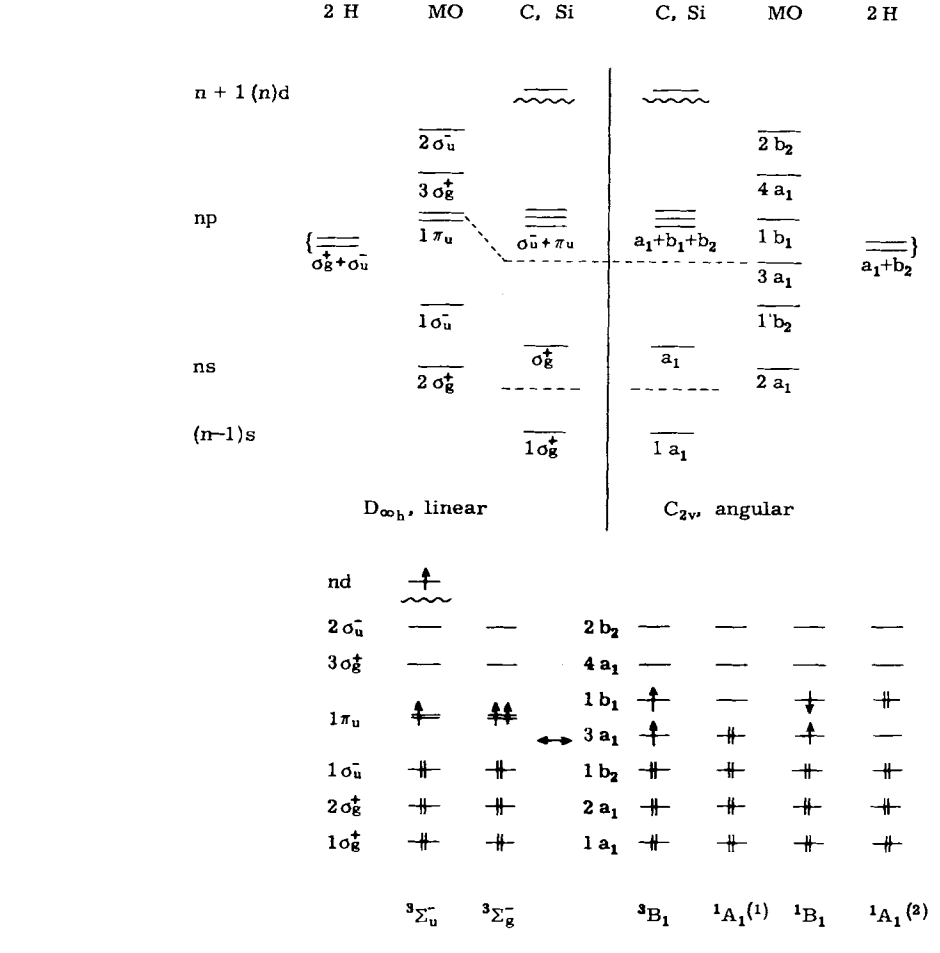
CH_2 and SiH_2

Apart from quite obvious structural differences between divalent carbon and divalent silicon there are some minor ones which may be detected only upon thorough investigation. Compounds of C and Si with H and O exhibit more obvious mutual deviations. For instance, the radicals CH_2 and SiH_2 generated by flash photolysis of CH_2N_2[13] and $C_6H_5SiH_3$[14] or by low temperature photolysis of SiH_4[15] differ considerably in geometry and electronic structure.

Table 3. Ground and excited states of CH_2 and SiH_2 [14, 15].

		Excitation energy T[cm^{-1}]	∢ HXH [°]	r XH [Å]	Configuration
CH_2 Ground state	X^3B_1	±0	≈140	≈1.07	$(2a_1)^2(1b_2)^2(3a_1)(1b_1)$
	$a^1A_1^{(1)}$	x≤8000	$102._4$	1.11_1	$(2a_1)^2(1b_2)^2(3a_1)^2$
	b_1B_1	x+7100	140±15	1.05_3	$(2a_1)^2(1b_2)^2(3a_1)(1b_1)$
	$c^1A_1^{(2)}$	≤x+27700			$(2a_1)^2(1b_2)^2(1b_1)^2$
	$B^3\Sigma_u^-$	70634	180	1.029 [a]	$(2\sigma_g)^2(1\sigma_u)^2(1\pi_u)(3d\pi_g)$
SiH_2 Ground state	$X^1A_1^{(1)}$	±0	92.1	1.521	$(2a_1)^2(1b_2)^2(3a_1)^2$ [b]
	A^1B_1	(≈15550)	122	1.48	$(2a_1)^2(1b_2)^2(3a_1)(1b_1)$
SiH_2, calculated [16]	$X^1A_1^{(1)}$	±0	95.4		$(2a_1)^2(1b_2)^2(3a_1)^2$
	$^1B_1$	20460	146.2		$(2a_1)^2(1b_2)^2(3a_1)(1b_1)$
	$^1A_1^{(2)}$	25700	127.5		$(2a_1)^2(1b_2)^2(1b_1)^2$
	$^3B_1$	16180	137.8		$(2a_1)^2(1b_2)^2(3a_1)(1b_1)$

[a] For CD_2.
[b] Only valence electrons considered.



Scheme 3. Electronic states of CH_2 and SiH_2.

Table 3 demonstrates that CH_2 has a nearly linear triplet ground state (X^3B_1), the HCH angle being $\approx 140°$; it was long assumed to be linear. In contrast, no triplet spectrum of SiH_2 has been observed so far, and in accord with matrix investigations[15] the singlet $^1A_1$ state ($\sphericalangle$HSiH 92.1°) is assumed to be the ground state. This bent state has been detected for CH_2 too; it lies $\leq 8000\,cm^{-1}$ above the X^3B_1 ground state and has an HCH angle of 102.4°. According to calculations by *Jordan*[16] this triplet state $^3B_1$ of SiH_2 is $16180\,cm^{-1}$ above the ground state. As SiH_2 is usually formed in an excited singlet state from which an allowed transition leads to the singlet ground state, detection of a triplet state is expected to be difficult. Scheme 3 depicts qualitatively the electronic structures of the different states.

Monomeric SiO_2 has not yet been studied extensively. A linear OSiO structure was deduced from the failure of a molecular beam of SiO_2 generated at 2500 °K to undergo deflection in an electrostatic quadrupole field[17]. Furthermore, divalent silicon is present in Si_2O_2 and Si_3O_3 formed from SiO at a few °K in N_2 and Ar matrices[14]. Infrared spectra including isotope shifts suggest a planar four-membered ring structure with D_{2h} symmetry for the dimer, the OSiO angle being 87°, and a planar six-membered ring with D_{3h} symmetry and an OSiO angle of 100° for the trimer. The SiO stretching force constants (≈ 3.6 mdyn/Å) correspond to a SiO single bond; cf. SiO ($^1\Sigma$) 9.0 mdyn/Å!

Investigations of the dihalides CF_2/CCl_2 and $SiF_2/SiCl_2$ are consistent with a common $^1A_1$ ground state characterized by an angle of approximately 100°, which is considerably widened in a singlet upper state. The widening in the excited $^1B_1$ state is obvious from the progression of the $^1A_1 \rightarrow {}^1B_1$ electronic transition with ν_2' ($250\,cm^{-1}$ in SiF_2, $201\,cm^{-1}$ in $SiCl_2$), the bending frequency of the $^1B_1$ state. However, the geometry of the excited states has not yet been accurately determined[18].

A similar widening upon electronic excitation $A' \rightarrow A''$ occurs for HSiX species (X = Cl, Br, I)[19]. This widening is smaller than that observed upon excitation of HCF and HCCl[20]. In both cases the excitation causes a strengthening of the CX and SiX bonds (Table 4). Again the widening of the bond angle is apparent in the electronic spectrum from the extended progression with ν_2', the bending frequency of the excited state. The linearization barrier is small and increases in the order HCCl, HCF, HSiBr, HSiCl, not exceeding a height of $2250\,cm^{-1}$ above the lowest vibrational level for HCCl.

Table 4. Electronic states of HCF, HCCl, HSiCl, and HSiBr.

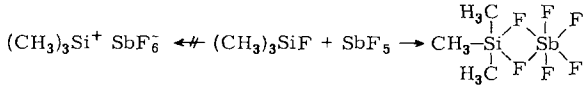
	HCF [20]	HCCl [20]	HSiCl [19]	HSiBr [19]
Ground state $^1A'(a'')^2(a')^2(a')^2$				
r HC(Si) [Å]	1.12_1	1.12	1.561	1.561
r XC(Si) [Å]	1.31_4	1.68_9	2.064	2.231
$\sphericalangle$ [ ]	101.8	103.4	102.8	102.9
ν_2'' [cm^{-1}]	1403.2		805.5	$771._4$
Excited state $^1A''(a'')^2(a')^2(a')(a'')$				
T_0 [cm^{-1}]	17287	12274 [a]	20717.6_5	19903.0_5
r HC(Si) [Å]	1.12		1.499	1.499
r XC(Si) [Å]	1.29_7		2.047	2.208
$\sphericalangle$ [ ]	127.2	135	116.1	116.6
ν_2' [cm^{-1}]	1021.3	860	$563._7$	$535._1$

[a] For DCCl.

In conclusion, comparable compounds of C and Si exhibit both structural similarities and specific differences. One should, however, keep in mind that the chemistry of sp hybridized carbon has no silicon counterpart.

4. Silicon with CN 3

Similarly, differences are apparent between species of trivalent carbon and silicon. So far no chemistry of sp^2 hybridized silicon has been established: in contrast to C, Si prefers to adopt a CN of 5 with sp^3d structure arising from d orbital participation. A "sp^3d" complex is formed instead of $(CH_3)_3Si^+$ if $(CH_3)_3SiF$ in SO_2FCl is treated with an excess of SbF_5[21].



Carbonium ions may easily be prepared and analyzed under similar conditions.

4.1. Silyl Radicals

Compared with silicenium ions (not obtained so far), radicals like $R_3Si^{\cdot}$ are of greater importance. They too differ considerably from their carbon analogs, as do also the conditions under which they are formed. As discussed in detail by *Davidson*[22], radical formation by hydrogen abstraction or by pyrolysis, yielding olefin-like $p\pi p\pi$ bond systems, is less favored for silicon than for carbon which, in contrast to silicon, tends to form $p\pi p\pi$ double bonds.

A structural difference is observed between the simplest radicals CH_3 and SiH_3. The planarity of $^{\cdot}CH_3$, which is hardly in doubt[23], confirms predictions[24] which in turn suggest a pyramidal geometry for $^{\cdot}SiH_3$. This suggestion has been experimentally proved for $^{\cdot}SiH_3$ radicals prepared by different reactions. A pyramidal structure has been deduced both from nuclear coupling constants $A(^{29}Si)$ (dependent on hybridization) of $^{\cdot}SiH_3$ obtained on γ irradiation by ^{60}Co of SiH_4 in Xe and Ar matrices[25] and an infrared investigation of $^{\cdot}SiH_3$ obtained on vacuum UV photolysis of SiH_4 in a matrix[15]. A p:s ratio of 5.2 to 5.7 for the free electron corresponding to a pyramidal angle of 15 to 16° or a bond angle of 113—114° has been derived from ESR spectra of the series of $(CH_4)_nSiH_{3-n}$ radicals[26]. A slight flattening of the radicals may however be discerned as n increases, the flattening being more pronounced for radicals like $(CH_3)_3SiSi(CH_3)H$ and $(CH_3)_3SiSi(CH_3)_2$.

4.2. Halosilyl Radicals

While the structures of CH_3 and SiH_3 differ considerably, no similar differences have so far been observed for

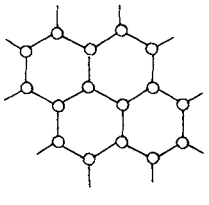
CF_3/SiF_3 and $CCl_3/SiCl_3$. All these radicals are pyramidal with bond angles near to 109° 28′, but further interpretation of the data reported for CF_3 (ESR, matrix IR, rapid scan IR following flash photolysis[27]), SiF_3 (matrix IR of vacuum UV photolyzed products[28]), CCl_3 (matrix IR[29], bond angles not very certain), and $SiCl_3$ (matrix IR[30]) is not yet justified.

Besides the X_3Si radicals, the X_3Si^- anions are of interest. While the structure of the known $SiCl_3^-$ anion has not been reported, the silyl derivatives of the alkali metals $KSiH_3$, $RbSiH_3$, and $CsSiH_3$ have been studied by X-ray diffraction and broad line NMR[31]. A HSiH bond angle of $94\pm4°$ was deduced assuming a SiH distance of 1.48 Å. Comparison with the HCH angle of $LiCH_3$ and KCH_3 is of limited significance: the CH_3 groups are likely to be pyramidal in both compounds[32] and, in view of the well-known difficulties in determining hydrogen positions by X-ray diffraction, the value of $111\pm8°$ for the HCH angle of $LiCH_3$ appears rather uncertain.

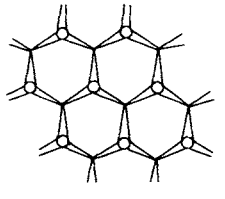
4.3. Silicon and Silicides

Silicon's inability to form an sp^2 hybrid is also observed for the element itself, which has the diamond structure and fails to form a graphite analog. Lepidoid, layer-like silicon obtained from $CaSi_2$ is not considered to be an analog of graphite because it consists, like $CaSi_2$, of puckered Si_6 rings.

Nevertheless CN 3 is by no means rare in silicides. On the one hand, planar, graphite-like $(Si)_\infty$ units have been observed, *e.g.* for β-USi_2 *(4A)*, and on the other, the puckered $(Si)_\infty$ structure corresponding to $CaSi_2$ *(4B)*, three-dimensional crosslinking as in $ThSi_2$, and finally 2- and 4-atomic $(Si)_m^{x-}$ units *(4C, 4D)*, including their derivatives of "molecular" size, have also been reported. In contrast, ionic carbides prefer C^{4-} or C_2^{2-} structures[34].



ß–USi_2 *(4A)*



$CaSi_2$, As *(4B)*

(2.48 Å) (2.51 Å)

$^{\ominus}:C\equiv C:^{\ominus}$

1.20 Å

$:N\equiv N:$

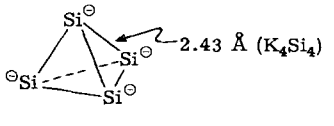
1.10 Å

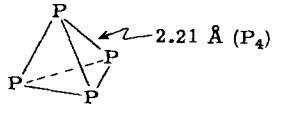
Si — Si

2.30 Å (U_3Si_2)[33]

2.37 Å (Li_2Si)

(4C)





(4D)

Generally a close relationship to the isoelectronic neighboring elements is evident; thus CaSi, SrSi, and BaSi exhibit a $(Si^{2-})_\infty$ zigzag chain structure corresponding to $(Se)_\infty$[35].

The structural relationship between Si_4^{4-} (Ba_2Si_4, K_4Si_4) and P_4 is also apparent from the vibrational spectra[36]. The tetrahedral anions $(4K^+)Si_4^{4-}$ and $(4K^+)Ge_4^{4-}$ resemble P_4 and As_4 in giving infrared absorptions corresponding to F_2 vibrations. Table 5 lists the observed frequencies and the derived force constants. The close relationship of C_2^{2-} to N_2 and of Si_4^{4-} and Ge_4^{4-} to P_4 and As_4 is clearly demonstrated by their vibrational spectra.

Table 5. Parameters of molecules and ions.

	r MM [Å]	ν MM [cm^{-1}]	f MM [mdyn/Å]
N_2	1.10	2330	22.4
C_2^{2-}	1.20	2240	17.7
P_4	2.21	461 (F_2)	2.04
As_4	2.435	250	1.49
Si_4^{4-}	2.46	334/359	1.05
Ge_4^{4-}	2.56	188/202	0.87

5. Silicon with CN 5

Carbon involved in five or more individual bonds is assumed to occur only in transition states of short lifetime. In contrast carbon with CN >4 may be stabilized by polyelectronic polynuclear systems with particular bond properties, *e.g.* carbides, $CRu_6(CO)_{17}$ (C in the center of a Ru_6 cluster), and carboranes (*e.g.* $C_2B_{10}H_{12}$ in which carbon occupies two vertices of an icosahedron).

Consequently the specific chemistry and structure of compounds in which silicon forms 5 or 6 individual bonds is not analogous to that of carbon derivatives, but related to the behavior of heavier group IV homologs and some transition metals.

The ready formation of penta- and hexa-coordinate Si is usually ascribed to the accessibility of low-lying d orbitals. These extra orbitals should enable the number of σ bonds to exceed 4, lower the energy of transition states, thus accelerating reactions, participate in intramolecular dπpπ bonding, and finally diminish the energies of electronic transitions and facilitate formation of radicals by taking up an electron[1].

The following representative topics have been selected from the chemistry of pentacovalent silicon. The anion SiF_5^- which is isoelectronic with PF_5 has been reported. It may be isolated as $[Ph_4As][SiF_5]$[37] which is isostructural with $[Ph_4As]I$. All fluorine atoms appear to be equivalent in the ^{19}F-NMR spectrum due to exchange processes. In aqueous solution rapid hydrolysis is observed, forming species with a CN of 6[38]. Similar behavior has been reported for alkyltetrafluoro- and dialkyltrifluorosilicates $RSiF_4^-$ and $R_2SiF_3^-$.

The structure of SiF_5^- is assumed to be trigonal-bipyramidal, resembling PF_5, and this geometry has been observed throughout for Si with CN 5: in pentameric $[(CH_3)_2NSiH_3]_5$ *(5A)* with an essentially planar ten-mem-

bered $(SiN)_5$ ring[39], in the 1:1 adduct of $N(CH_3)_3$ and $SiCl_4$ *(5B)*[40], and in the silatranes.

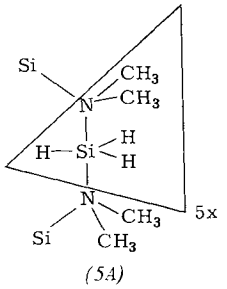
An interesting group of chelate compounds deriving from triethanolamine are called silatranes *(5C)*[41]. In these compounds three oxygen atoms or one carbon and two oxygen atoms occupy equatorial positions, and the forth ligand Z and the nitrogen atom occupy axial sites of a trigonal bipyramid. The order of the coordinative SiN bond (which is less than unity throughout) and the angle α (which amounts to 90° for an undistorted trigonal bipyramid) are governed by the nature of the ligand Z. Some structural data of silatranes are reproduced in Table 6.

Table 6. Structural data of silatranes.

Z	N(CHRCHRX-)$_3$	*r* SiN [Å]	α [°]	Ref.
m-$O_2NC_6H_4$	$N(CH_2CH_2O-)_3$	2.116	95.8	[42]
C_6H_5	$N(CH_2CH_2O-)_3$	2.193	97.1	[43]
C_6H_5	$N(o\text{-}C_6H_4O-)_3$	2.334	100	[44]
CH_3	$N(CH_2CH_2O)_2(CH_2CH_2CH_2)$	2.336	100	[45]

Distortion of the trigonal bipyramid arises by simultaneous lengthening of the SiN bond and widening of α. The trigonal bipyramidal arrangement is also preferred by bis(*o*-phenylenedioxo)phenylsilicate *(5D)*, the axial SiO bonds (1.794 Å) being considerably longer than the equatorial ones (1.700 Å)[46]. An intramolecular coordination of a Lewis base atom affording pentacoordinate silicon similar to the situation in silatranes has been established for cyclobis(benzamidodimethylsilane) *(5E)*. The exocyclic SiO contact of 2.613 Å is however comparatively long and the bond is weaker than that between Si and N in the silatranes[47].

The silicon atom may participate in two-electron three-center bonds of boranes[48], bridge two transition metal atoms, or form M···H···Si bonds. Recent structure determinations by X-ray diffraction of *(5F)* and *(5G)* established the position of all atoms, but were not able to clarify whether additional direct SiM bonds appear along with the hydrogen bridges[49]. Obviously the valence bond approach fails to provide an adequate description of the bonding in these compounds.



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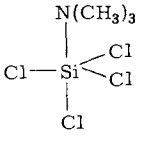
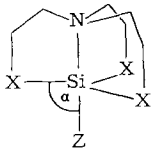


(5B)



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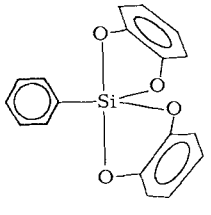
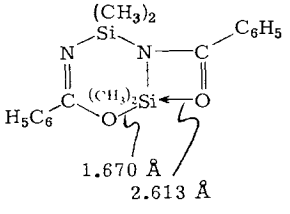
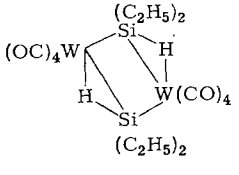


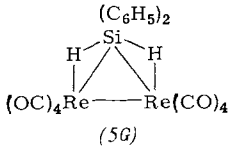
(5D)



(5E)



(5F)



(5G)

6. Silicon with CN 6

Substitution reactions at a tetracovalent carbon or silicon atom frequently proceed *via* a pentacovalent intermediate; further expansion of the coordination sphere is not likely to occur.

However, *Corriu* and *Leard*[50] were able to demonstrate that an optically active triorganochlorosilane $R^1R^2R^3SiCl$ in inert solvents is racemized by Lewis bases such as Me_2NCHO, $(Me_2N)_3PO$, or Me_2SO, the process following second order kinetics. This suggests involvement of a hexacovalent intermediate, probably with octahedral structure.

CN 6 is favored if a silicon atom is linked to several halogen atoms such as F and Cl. This CN is achieved *e.g.* by addition of halide ions ($\rightarrow SiF_6^{2-}$) or suitable Lewis bases with O, N, or P atoms.

The octahedral SiF_6^{2-} ion is readily formed; it decomposes to SiF_4 and 2 HF when heated in acidic aqueous solution. A comparison of SiF bond lengths and force constants for different coordination numbers of Si merits attention (Table 7). The strongest ground state SiF bond is observed in SiF_4.

Table 7. Properties of SiF bonds.

Molecule/ion	*r* SiF [Å]	*f* SiF [mdyn/Å]	Ref.
SiF ($X^2\Pi_r$)	1.600	4.9	[5]
SiF_2	1.591	5.0	[51]
SiF_3	1.56	5.5	[28]
SiF_4	1.55	6.3	[3]
SiF_6^{2-}	1.66...1.71	3.5	[3, 52]

Tetrahalides may direct two added Lewis base atoms into *cis* and *trans* positions; both types of coordination have been established in silicon chemistry. Geometric requirements of the ligand force SiF_4·bipyridyl (bipy) into a *cis* configuration[53], while SiF_4·2 pyridine (py)[54] adopts a *trans* arrangement of the ligands. Table 8 presents some data on $Si(Hal)_4L_2$ complexes.

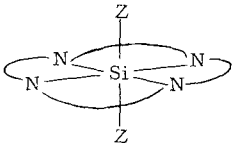
The *cis*-SiF_4L_2 adducts exhibit two different types of SiF bonds; those which are *trans* to L are the shorter ones

Table 8. $Si(Hal)_4L_2$-type complexes.

Compound	Geometry	r SiHal [Å]	r SiL [Å]	Ref.
$SiF_4 \cdot 2py$	*trans*	1.64	1.93	[54]
$SiF_4 \cdot bipy$	*cis*	1.66 (2×)	1.98	[53]
		1.63 (2×)		
$SiF_4 \cdot 2NH_2R$	*cis*	?	?	[55]
(R = H, CH_3, NH_2)				
$SiCl_4 \cdot 2py$	*trans*	?	?	[56]
$SiCl_4 \cdot 2P(CH_3)_3$	*trans*	2.20	2.26	[57]
		2.30		
$SiBr_4 \cdot 2P(CH_3)_3$	*trans*	?	?	[40]

in $SiF_4 \cdot bipy$. Two pairs of F atoms which show different reactivities on reaction with silylamines may be recognized in $SiF_4 \cdot 2NH_3$, contrasting in this respect with *trans*-$SiF_4 \cdot 2py$[58].

In complexes formed by tetradentate ligands, as in Si porphyrins or Si phthalocyanines[59,60], the geometry is governed by the planar macrocycle; the free coordination positions are axial *trans* and may be occupied by —F, $-OSiR_3$ *(6A)*, or (—O—)/2 *(6B)*. In the latter case, the Si phthalocyanine fragments are arranged in layers, the SiO distance of 1.659 Å being half the distance between two layers.



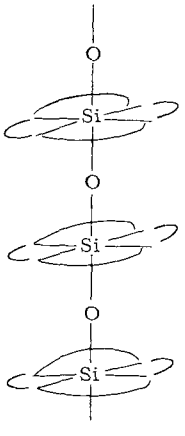
(6A)

macrocycle: porphin

Z = F, $OSiR_3$[59]

macrocycle: phthalocyanine

Z = $OSiR_3$[60]



(6B)

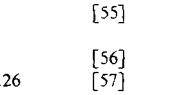
$(PcSiO)_x$[61]

The silicon atom usually prefers CN 4 if linked to oxygen atoms, but exceptions such as thaumasit and high pressure modifications of SiO_2 are known. Tetrahedral SiO_4 units are common to the great majority of silicates, which form different types by different crosslinking.

In this context, it is significant that silicon diphosphate SiP_2O_7 has a structure in which each Si atom is coordinated by six O_3POPO_3 groups. On the other hand, all six terminal O atoms of the O_3POPO_3 groups are joined to different Si atoms. This structure may be interpreted in terms of SiO_6 octahedra sharing corners with PO_4 tetrahedra[62]; the POP angle is approximately 139°.

The octahedral (Table 9) is longer than the tetrahedral SiO distance. In general, long and relatively weak bonds are characteristic for Si with CN 6; in this respect the element differs somewhat from its neighbors P and S.

Table 9. SiO distances [Å] for CN 4 and CN 6.

SiO_4^{4-}	1.60	[63]
$Si(OCH_3)_4$	1.64	[3]
$[PcSiO]_x$ [a]	1.659	[61]
SiP_2O_7	1.74–1.79	[62]
	1.765–1.813	[63]

[a] Pc = Phthalocyanine.

7. Unusual Structural Parameters of Tetracovalent Silicon

Silicon contrasts with carbon not only in its coordination chemistry but also because it can induce specific structural and chemical properties in groups to which it is linked. This ability is particularly pronounced when it is bonded to N and O; however, derivatives of heavier elements behave quite normally in this respect.

7.1. Bonding Properties

The electronegativity of silicon would suggest that it attracts bonding electrons in bonds to C, N, O, and F less than carbon; consequently SiOH and SiNH compounds should be weaker acids than corresponding COH and CNH compounds, while O and N, when linked to Si, should exhibit stronger Lewis base properties.

The reverse is observed. An interpretation assuming back bonding $\ddot{X}—Si \leftrightarrow \overset{\curvearrowright}{\ddot{X}}—Si \leftrightarrow \overset{\oplus}{\ddot{X}}=\overset{\ominus}{Si}$ of (p→d)π type has proved useful. According to this, the lone pair of the X atom, preferably of p character, interacts with Si d orbitals of suitable symmetry, thus reducing the electron density at X and strengthening the XSi bond.

While some of the consequences for chemical properties at the X atom will be discussed in Chapter 8, some structural aspects caused by the specific action of the Si atom are dealt with here.

In a discussion of bonding between X and Si one should distinguish between two effects. Firstly, there is rehybridization to produce high p character in lone pairs on X induced by the Si atom. Secondly, there is the amount of π bonding reflected by SiX bond shortening or equivalent parameters. Both phenomena, though independent, are usually observed to occur simultaneously. Thus (p→d)π strengthening is possible for pyramidal $N(SiH_3)_3$ without rehybridization, though it is less effective than for a planar molecule.

7.2. Bond Angles

Structural data so far available indicate that unusual bond angles occur only for SiN and SiO compounds. A precise structural determination of disilylmethane, however, revealed that even carbon uses s-rich orbitals for its bonds to silicon[64], and the same arguments hold for the planarity of the $(Me_3Si)_3C^{\cdot}$ radical, deduced from ESR spectroscopy[65].

Table 10 presents some typical bond angles for simple silyl compounds and compares them, as far as possible, with analogous C and Ge derivatives.

Table 10. SiXSi bond angles: comparison with C and Ge compounds.

Compound	∢ [°]	Ref.	Compound	∢ [°]	Ref.
$H_3Si-CH_2-SiH_3$	114.4	[64]	$H_3C-CH_2-CH_3$	112.4	[64]
$H_3Si-O-SiH_3$	144.1	[68]	$H_3C-O-CH_3$	111.5	[67]
$H_3Si-O-CH_3$	120.6	[66]	$H_3Ge-O-GeH_3$	126.5	[69]
$H_3Si-NH-SiH_3$	127.7	[70]	$H_3C-NH-CH_3$	111±3	[67]
$(H_3Si)_3N$	119.7	[71]	$(H_3C)_3N$	110.6	[64]
			$(H_3Ge)_3N$	120	[72]
$H_3Si-S-SiH_3$	97.4	[73]	$H_3C-S-CH_3$	98.9	[69]
			$H_3Ge-S-GeH_3$	98.9	[69]
$(H_3Si)_3P$	96.45	[74]	$(H_3C)_3P$	99.1	[67]
			$(H_3Ge)_3P$	95.39	[75]

The exceptional behavior of O and N is obvious, while analogous sulfur and phosphorus compounds behave normally, like alkyl derivatives, with respect to the angles at S and P and to the Lewis basicity of the lone pair(s). This view is supported by the fact that the inversion barrier of trivalent phosphorus, though small, corresponds exactly to the value predicted for phosphanes from the group electronegativity of the substituents[76].

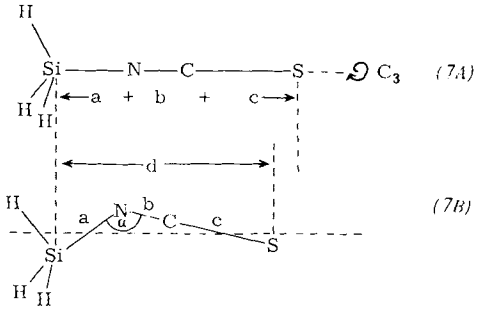
Nitrogen is invariably planar when linked to two or three Si atoms, as in $(H_3Si)_2NH$[70], $(H_3Si)_2NCH_3$, $(H_3Si)_2NBF_2$, $(H_3Si)_2NN(SiH_3)_2$[77], and corresponding trimethylsilyl compounds; see also Section 8. However, a single silyl group will not always flatten nitrogen, as has been demonstrated by $(CH_3)_2NSiH_3$: the SiN bond is tilted out of the CNC plane by 27.8°[78]. In contrast, planar nitrogen has been observed for $(CH_3)_2NSiF_3$ and $(CH_3)_2NSiCl_3$[79], and also for silylpyrrole[80] where the planarity favors participation in the delocalized π system (which is less pronounced, however, than for pyrrole itself[81]).

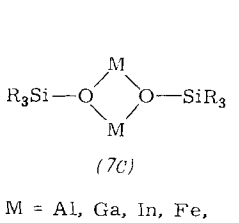
The bond angles at the X atoms are only slightly altered upon changing the substituents at the Si atom: $(H_3Si)_2NH$ (127.7°) and $(Me_3Si)_2NH$ (125.5°)[82] differ in their SiNSi angles by only 2.2° (only slightly greater than the experimental error), while the SiOSi angle increases from 144.1° in $(H_3Si)_2O$ and 146° in $(Cl_3Si)_2O$[83] to 155.7° in $(F_3Si)_2O$[84], the increase corresponding to an enhancement in the s character of the bonding electrons of oxygen from 44.7 to 47.6%.

The SiNSi bond angle in $(H_3Si)_3N$ was found by electron diffraction to be slightly smaller than 120°. This is, however, not equivalent to deviation from planarity because the angle is averaged over molecules in different phases and occupying different levels of the Si_3N out-of-plane bending vibration. Only an infinitely small number is passing through the equilibrium (planar) structure at any given moment.

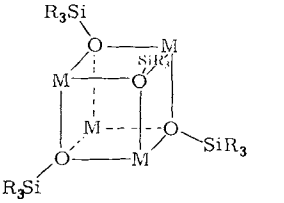
7.3. Pseudohalides

Structural parameters obtained by averaging over molecules in different vibrational states are particularly interesting for pseudohalides because high excited levels of low-lying bending vibrations are occupied in these molecules. Consequently the average molecule of, *e.g.*, H_3SiNCS, will not have the equilibrium structure *(7A)*, but at the moment of electron diffraction exhibits shrinkage *(7B)*; *d* will be smaller than $a+b+c$.





M = Al, Ga, In, Fe, Au[99,100]



M = alkali metal, CH_3Be, RHg, RZn, RCd[100,101]

Table 11 presents the bond angles α for some silyl and methyl pseudohalides and quotes the method by which they were determined. The figures clearly indicate that the angles sometimes differ less between analogous silicon and carbon compounds than for the same compounds when different methods of investigation are used. Nevertheless, comparison of microwave data obtained for H_3SiNCS and H_3CNCS indicates the special behavior of silicon. In this context it should be pointed out that the differences mentioned so far do not reflect experimental uncertainties of the structural investigations but are due to the specific relation between the speed of the method used and that of the intramolecular motions.

The SiOSi bond angle is always smaller than 180°, but greater than 120° in the molecules mentioned so far; however, it was found to be actually 180° in $Ba_3Si_4Nb_6O_{26}$ and $Ba_3Si_4Ta_6O_{26}$[92].

Table 11. SiNC and CNC angles α in pseudohalides.

Compound	α [Å]	Method [a]	Ref.
H_3SiNCO	180	MW	[85]
	151.7	ED	[85]
F_3SiNCO	160.7	ED	[85]
Cl_3SiNCO	138.0	ED	[86]
$(CH_3)_3SiNCO$	150	ED	[87]
$Si(NCO)_4$	180	IR/Ra	[88]
	146.4	ED	[88]
H_3CNCO	139.98	MW	[89]
H_3SiNCS	180	MW	[90]
	163.8	ED	[91]
$(CH_3)_3SiNCS$	154	ED	[87]
$Si(NCS)_4$	172.5	X	[91]
H_3CNCS	147.46	MW	[89]

[a] MW = microwave spectroscopy, ED = electron diffraction, X = X-ray structural analysis, IR/Ra = IR/Raman spectroscopy.

If a siloxy group is linked to electropositive, coordinatively unsaturated atoms, the oxygen atom usually becomes three-coordinated, while remaining bonded to one single Si atom. Four-membered ring *(7C)* or cubane structures *(7D)* are most favored.

Quite a number of monomeric silanolates are also known, among which $Me_3SiOReO_3$ ($\measuredangle$SiORe 164°) and $(Ph_3SiO)_2CrO_2$ ($\measuredangle$SiOCr 133.1 and 162.7°) have been characterized by structural analyses[93].

7.4. Distances

Judging by distances, an increase in bond orders by (p→d)π overlap occurs for SiN, SiO, SiF, and presumably SiCl bonds. However, a qualitative estimation of the extent of π bonding from the bond shortening is difficult for several reasons. Firstly the single bond reference length can only be estimated, and secondly it is well known that, as in carbon compounds, electronegative substituents and increased s character operate in the sense of bond strengthening. Table 12 lists some typical SiX distances and compares them with the expected values.

Table 12. Typical SiX distances [Å].

SiC 1.88 [a]	
$(CH_3)_3Si{-}C{\equiv}CH$ 1.825 [93]	$H_3Si{-}CH{=}CH_2$ 1.853 [3]
H_3SiCH_3 1.8669 [3]	
SiN 1.80 [a]	
Cl_3SiNCO 1.646 [86]	$(Cl_2SiNH)_3$ 1.68 [94]
$(H_3Si)_3N$ 1.734 [71]	$[(CH_3)_3Si]_2NH$ 1.735 [84]
$\{[(CH_3)_3Si]_2N\}_3Al$ 1.75 [95]	
SiO 1.76 [a]	
$Ba_3Si_4Nb_6O_{26}$ 1.599/1.629 [92]	$(H_3Si)_2O$ 1.634 [68]
H_3SiOCH_3 1.640 [66]	$[(CH_3)_2SiO]_4$ 1.65 [97]
SiF 1.69 [a]	
SiF_4 1.54 [3]	$HSiF_3$ 1.561 [3]
H_3SiF 1.593 [96]	
SiSi 2.34 [a]	
Si_2H_6 2.32 [3]	
SiP 2.24 [a]	
$(H_3Si)_3P$ 2.248 [74]	H_3SiPH_2 2.249 [98]
$H_3SiP(CH_3)_2$ 2.245 [98]	
SiCl 2.05 [a]	
$SiCl_4$ 2.01 [3]	H_3SiCl 2.049 [96]

[a] Sum of covalent radii, corrected according to *Schomaker-Stevenson*.

SiN, SiO, and SiF bonds reveal their exceptional properties in two respects: on the one hand the distances are shorter by 0.1 to 0.15 Å than expected for single bonds, and on the other hand they are systematically sensitive to substituent effects, contrasting with the angles in this respect. Normal behavior is demonstrated by various silylphosphanes.

8. Unusual Aspects of Coordination and Stability

Experiments have shown that the Lewis base strength of oxygen and nitrogen drops considerably upon silyl substitution. Addition of Lewis acids to SiO and SiN compounds or quaternation of nitrogen in silylamines are only achieved in exceptional cases; siloxonium compounds, however, which possess the $R_3SiO<$ fragment have been met with in Section 7. Due to their reduced Lewis base strength $SiNR_2$ and SiOR derivatives are extremely useful for the transfer of NR_2 and OR groups in cases where HNR_2 or HOR would undergo addition rather than substitution. In particular, transition metal halides easily enter into the following reactions:

$$TiCl_4 + Me_3SiNR_2 \rightarrow Me_3SiCl + R_2NTiCl_3$$
$$WF_6 + n\,Me_3SiOR \rightarrow n\,Me_3SiF + (RO)_nWF_{6-n}$$

In this context the detection of the bis(trimethylsilyl)oxonium ion $(Me_3Si)_2OH^+$ in mixtures of $(Me_3Si)_2O$ and "magic acid" ($HSO_3F/SbF_5/SO_2$) is particularly noteworthy[103]. Also contrary to expectation, silylammonium salts could be isolated from the following reactions[104]:

$$Me_3SiCo(CO)_4 + Me_3N \rightarrow [Me_3SiNMe_3]^+[Co(CO)_4]^-$$
$$Me_3SiNMe_2 + HCo(CO)_4 \rightarrow [Me_3SiNHMe_2]^+[Co(CO)_4]^-$$

Though silyl derivatives of most metals have been obtained during the last few years, they do not display any unexpected structural features apart from strong substituent effects. They resemble the alkyl compounds in many respects, quite often exhibiting steric effects similar to those of the *tert*-butyl group. Among the compounds not stabilized by extra ligands $Hg(SiMe_3)_2$, $In(SiMe_3)_3$, and $Tl(SiMe_3)_3$ should be noted. They are reported to be monomeric, volatile, and thermally rather unstable[105].

Unusual bonding and coordination numbers occur however when a metal and silicon are connected by nitrogen or carbon bridges; metal silanolates may also exhibit this particular behavior.

8.1. Metal Bis(silyl)amides

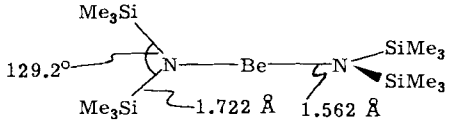
In many cases metals M exhibit their lowest CNs ever observed (2, 3) in metal bis(silyl)amides $[(R_3Si)_2N]_xM$. These compounds may be obtained without difficulty from metal halides and alkali metal bis(silyl)amides[106]; due to their molecular size as monomers (except for alkali metal and Cu derivatives) they also number among the most volatile metal compounds.

Sterically, a metal atom M is perfectly shielded by two or more $(R_3Si)_2N$ groups. At the same time it may, at least in part, increase its effective electron number by participating in the NSi_2 (pπdπ) system. Available structural and spectroscopic investigations establish the planarity of the overall $MNSi_2$ bond system in which M has a geometry corresponding to its CN: MN_2 linear, MN_3, LMN_2, and L_2MN trigonal planar. Alkali metal bis(silyl)amides possessing a formally monovalent metal atom are associated, becoming increasingly ionic from Li to Cs; a CN 1 has not yet been established for these compounds. They add Lewis bases such as ether or dioxane. $LiN(SiMe_3)_2$ (115 °C/1 torr) and $NaN(SiMe_3)_2$ (202 °C/2 torr) may be distilled without decomposition[106]. $LiN(SiMe_3)_2$ easily changes its degree of association, being obviously dimeric in solution, but forming a trimer in

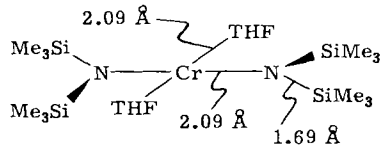
the solid state which consists of a planar $(LiN)_3$ six-membered ring with a SiNSi angle of 118°[102]. According to spectroscopic investigations the SiNSi angle widens to ≈140° as the ionic character increases. It was found to be 136° in $KN(SiMe_3)_2 \cdot 2$dioxane, in which the K atoms are pentacoordinated by N and four O atoms of different dioxane molecules[107].

8.2. Metal Bis(disilylamides)

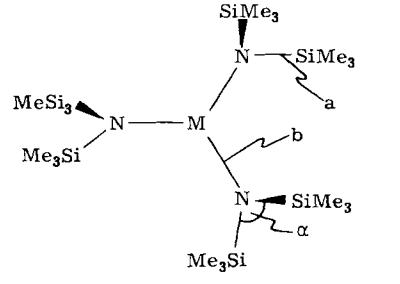
A CN of 2 is rather unusual for metals, being known only for Zn, Cd, Hg, Cu, and Ag. However, the bis(trimethylsilyl)amido group stabilizes this coordination number not only for Zn, Cd, and Hg, but also for many other metals. Table 13 lists some monomeric metal bis(disilylamides).



(8A)



(8B)



(8C)

M = Al: a=1.75 Å, b=1.78 Å, α=119.5°; [95]
Θ(∢ Si_2N/MN_3)=50°

M = Fe: a=1.73 Å, b=1.92 Å, α=121.24°; [115]
Θ=49°

Table 13. Metal bis(disilylamides).

Compound	M. p. [°C]	B. p. [°C/torr]	Color	μ_{eff} [μ_B]	Ref.
$[(Me_3Si)_2N]_2Be$ *(8A)*	−3 to −1	110/3	colorless	diam.	[108]
$[(Me_3Si)_2N]_2Zn$	12.5	82/0.5	colorless	diam.	[109]
$[(Me_3Si)_2N]_2Cd$	8	93/0.5	colorless	diam.	[109]
$[(Me_3Si)_2N]_2Hg$	11	78/0.15	colorless	diam.	[109]
$[(Me_3Si)_2N]_2Cr \cdot 2THF$ *(8B)*				4.93	[110]
$[(Me_3Si)_2N]_2Mn$	>20	100/0.2	pink		[111]
$[(Me_3Si)_2N]_2Co$	73	101/0.6	green	4.83	[112, 113]
$[(Me_3Si)_2N]_2CoPPh_3$	dec. >90			4.84	[113]
$[(Me_3Si)_2N]_2Ni$	<20	80/0.2	red		[111]

Linear NMN fragments have been established for M = Be *(8A)*[114], Zn, Cd, Hg[109], Cr *(8B)*[110], and Co[112]; furthermore they will probably be present if M is Mn or Ni. *(8B)* may be expected to have a tetrahedral or distorted octahedral structure; the observed square planar *trans* arrangement in which chromium can use dsp^2 hybrid orbitals is consistent with the reported value of four unpaired electrons. $[(Me_3Si)_2N]_2CoPPh_3$ and $(Me_3Si)_2NNi(PPh_3)_2$ (μ_{eff} 1.91 μ_B) possessing planar N_2CoP and $NNiP_2$ units respectively are examples of CN 3, which is very uncommon for Co and Ni[113].

8.3. Metal Tris(disilylamides)

Similarly CN 3 is far from common in the coordination chemistry of metals. Nevertheless such a coordination number appears in many metal tris(disilylamides), which at the same time will not add any further ligand [except in *(8D)*]. All $M[N(SiMe_3)_2]_3$ compounds obtained so far are isostructural, and planarity of the MN_3 and $MNSi_2$ fragments has been established by X-ray diffraction for M = Al, Cr, and Fe *(8C)*. Table 14 compares the tris(disilylamides) of various metals. Noteworthy is the high thermal stability which allows these compounds to be sublimed *in vacuo* (except for the Ti^{III} compound) despite their high molecular weights of about 530.

As in *(8B)* chromium has a formal oxidation state of +2 in $[(Me_3Si)_2N]_3CrNO$ *(8D)*[110], but a (nearly tetrahedral) trigonal pyramidal environment. Comparison of distances shows the CrN bonds to be considerably shorter in *(8D)* than in *(8B)*, strongly suggesting the presence of N→Cr pπdπ bonds enabling Cr^{II} to approach the [Kr] noble gas configuration.

Furthermore, comparison of *(8B)* and *(8D)* demonstrates that the formation of N→Mπ bonds cannot be the only reason for low coordination numbers of metal atoms and the high thermal stability observed. Probably both steric requirements of the ligands and a Lewis base strength of nitrogen, which is reduced by silicon and thus supresses nitrogen bridging, favor the formation and stability of monomeric bis- and tris(disilylamides).

8.4. Trimethylsilylmethyl Compounds

The last Section of the review is devoted to trimethylsilylmethyl compounds which have only recently attracted attention and appear to have initiated a most promising rapid development in silicon chemistry.

The lithium compound $(Me_3Si)_3CLi$, which decomposes at room temperature only after some weeks, belongs to this class of compounds[120]. When formulated as an ion the carbanion $(Me_3Si)_3C^-$ is isoelectronic with the nearly

Table 14. Metal tris(disilylamides).

Compound	Subl. temp. [°C/torr]	M.p. [°C]	Color	μ_{eff} [μ_B] [298 °K]	Ref.
$[(Me_3Si)_2N]_3Al$	< 120/0.5	188	colorless	diam.	[116]
$[(Me_3Si)_2N]_3Ga$	< 120/0.5	187	colorless	diam.	[116]
$[(Me_3Si)_2N]_3In$	< 120/0.5	168	colorless	diam.	[116]
$[(Me_3Si)_2N]_3Sc$	sublimable	172–174	colorless	diam.	[117]
$[(Me_3Si)_2N]_3Ti$	nonsublimable		blue	1.62	[117]
$[(Me_3Si)_2N]_3V$	$95/5 \times 10^{-3}$		brown	2.38	[117]
$[(Me_3Si)_2N]_3Cr$	$80/5 \times 10^{-3}$	120	green	3.74	[111, 117]
$[(Me_3Si)_2N]_3Fe$	$80/5 \times 10^{-3}$	135	green-black	5.94	[112, 115, 117, 118]
$[(Me_3Si)_2N]_3La$		145–149	colorless	diam.	[119]
$[(Me_3Si)_2N]_3Pr$		155–158	yellow-green	param.	[119]
$[(Me_3Si)_2N]_3Sm$	$75–100/10^{-4}$	155–158	yellow	param.	[119]
$[(Me_3Si)_2N]_3Eu$		159–162	orange	param.	[119]
$[(Me_3Si)_2N]_3Gd$		160–163	colorless	param.	[119]
$[(Me_3Si)_2N]_3Lu$		167–170	colorless	diam.	[119]

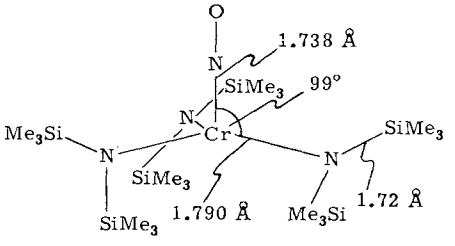
or entirely planar $(Me_3Si)_3N$ and may similarly be stabilized by resonance. The unusual properties of the $(Me_3Si)_3C^{\cdot}$ radical have been mentioned before in Section 4.1.

Stabilization of transition metal alkyls may in general be accomplished by ligands which undergo π bonding or by particular kinetic effects. Apart from having favorable steric properties, the CH_2SiMe_3 group prevents metal alkyls from decomposing by olefin elimination:

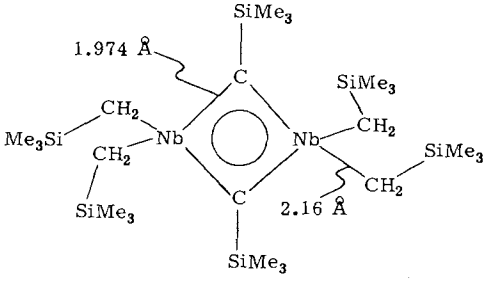
$$M{-}CH_2CH_2R \rightarrow MH + CH_2{=}CHR$$

The trimethylsilylmethyl derivatives of transition metals described recently are remarkable in several respects: they are thermally more stable than corresponding alkyls (if the latter are accessible at all) and make low CNs available for transition metals, thus partly resembling benzyl compounds. A selection of the monomeric, relatively volatile compounds is presented in Table 15. Some of them are very effective catalysts for the polymerization of α-olefins.

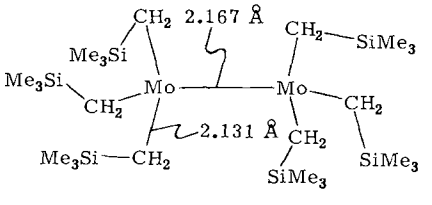
The $CSiR_3$ group may also be involved in bridging and in multiple bonding because of three free positions on the α-carbon atom. This makes possible the formation of a quasiaromatic MCMC four-membered ring system *(8E)*[122], in which MC distances in the ring are considerably smaller than the exocyclic bond lengths. On the other hand, compounds with MoMo and WW triple bonds may be obtained *(8F)*[123]; it is very likely that the last men-



(80) [110]



(8E) [122]



(8F) [123]

Table 15. Trimethylsilylmethyl compounds of some transition metals.

Compound	Subl. temp. [°C/torr]	M.p. [°]	Color	μ_{eff} [μ_B]	Ref.
$(Me_3SiCH_2)_3Se{\cdot}2THF$		62–63	colorless	diam.	[124]
$(Me_3SiCH_2)_3Y{\cdot}2THF$		48–50	colorless	diam.	[124]
$(Me_3SiCH_2)_4Ti$	$25/10^{-3}$	0–1	yellow-green	diam.	[124]
$(Me_3SiCH_2)_4Zr$	$25/10^{-3}$	10–11	colorless	diam.	[124]
$(Me_3SiCH_2)_4Hf$	$50/10^{-3}$	8–10	colorless	diam.	[124]
$(Me_3SiCH_2)_4V$		43	dark green	1.30 [a] 1.55 [b]	[121]
$(Me_3SiCH_2)_3VO$	$70/10^{-4}$	75	lemon yellow	diam.	[121]
$(Me_3SiCH_2)_4Cr$	$40/10^{-4}$	40	purple	2.89	[121]
$[(Me_3SiCH_2)_4Cr]^-$			blue-green	3.7	[121]
$[(Me_3SiCH_2)_2NbCSiMe_3]_2$ *(8E)*		152	red-brown	diam.	[122]
$[(Me_3SiCH_2)_2TaCSiMe_3]_2$ *(8E)*		170	orange		[122]
$(Me_3SiCH_2)_3MoMo(CH_2SiMe_3)_3$ *(8F)*	$100/10^{-4}$	99	yellow	diam.	[121, 123]
$(Me_3SiCH_2)_3WW(CH_2SiMe_3)_3$ *(8F)*	$120/10^{-4}$	110	orange-brown	diam.	[121, 123]

[a] Gouy method.
[b] NMR method.

tioned class of compounds has numerous surprises in store for us, especially in the field of homogeneous catalysis.

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Thermodynamics of Addition Polymerization Processes[**]

By K. J. Ivin[*]

The polymerizability of compounds such as 1,1-disubstituted ethylenes, aldehydes, ketones, isocyanates, and five- and six-membered ring compounds is determined largely by thermodynamic considerations. The transition from non-polymerizability to polymerizability, corresponding to a change in the sign of ΔG, is often quite sharp. Factors which generally make the free energy of polymerization more negative, and which therefore favor polymerization, are low temperature, high pressure, and high monomer concentration. Additional driving force is sometimes available if the monomer is in the supercooled (glassy) state rather than the crystalline state, or if the polymer crystallizes on formation. Alkyl substituents have an unfavorable effect on polymerizability; halogen substituents have a favorable effect. Many monomers which do not homopolymerize for thermodynamic reasons will copolymerize with a second monomer to the extent of forming copolymers containing 50 or even 66 mol per cent of the first monomer.

1. Introduction

α-Methylstyrene polymerizes at 0 °C yet does not polymerize at 100 °C[1], except at high pressure[2, 3]. α-Methoxystyrene copolymerizes readily with styrene but does not homopolymerize at any temperature[4]. Acetaldehyde can be made to polymerize either by lowering the temperature to below −40 °C or by raising the pressure at room temperature[5]. These are but three of the many observations in polymer chemistry that have a thermodynamic explanation. An understanding of the thermodynamics of polymerization processes is therefore of some importance to the preparative chemist in search of new polymers.

Three types of interwoven equilibria may be distinguished in addition polymerization systems:

1. equilibria between polymeric species;
2. equilibria between species which may be described as monomeric;
3. equilibria between monomeric and polymeric species.

Most polymers contain a multitude of chain lengths and a polymer in which all these species are present in their equilibrium proportions is said to possess the most probable, or thermodynamic distribution of molecular weights[6]. For long chain polymer the enthalpy per monomer unit is constant, so that equilibria of type 1 are governed solely by entropy considerations. The distribution in most polymers is determined by the kinetics of the process and generally (but not always) differs from the thermodynamic distribution[6]. The latter may be attained in time if there is available a reasonably fast mechanism, such as ester interchange[7], or reversible propagation in a "living" anionic system[8].

The best documented case of type 2 is provided by the siloxanes where oligomeric ring species can open to give the same high polymer. When the rings are above a certain size the heat of polymerization is effectively zero and the equilibria are again governed by entropy considerations. For type 3 equilibria, in contrast to types 1 and 2, the heat of reaction plays an important, often dominant, role in determining the position of equilibrium. We shall discuss a number of examples of this type of equilibrium and will later return to type 2 equilibria. We will finally consider the effect of reversible propagation steps on copolymer composition.

2. Addition Polymerization Considered as an Aggregation Process

The criterion for equilibrium for any chemical reaction at constant temperature and pressure is that the free energy change for the reaction, ΔG, shall be zero. Addition polymerization reactions differ, however, from all other types of reaction in that a large number of monomer molecules come together to form a single macromolecule. This gives to such reactions some of the features more usually associated with physical aggregation processes such as freezing. In particular there exists a sharp temperature, known as the "ceiling temperature", above which the formation of long-chain polymer does not occur, analogous to a melting point, above which the formation of macroscopic crystals does not occur. The essential feature common to both types of aggregation is that at a sharp temperature the free energy for the aggregation process is zero. In both cases the transition temperature is depressed by the addition of diluent, and is independent of the size of the aggregate except when this is very small.

The observation of a ceiling temperature[9] and the use of this term dates from 1938 although its thermodynamic explanation was not fully recognized until ten years later[10]. The reverse effect, that of a floor temperature, has long been known in the case of sulfur[11]: the formation of long chains only occurs above 159 °C. The complete generality of the ceiling temperature effect is illustrated in Table 1; a more complete list may be found in the Polymer Handbook[23].

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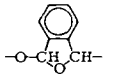
Table 1. Some observed ceiling temperatures T_c.

Monomer	Concn. (mol/l)	Solvent [a]	Polymer structure	T_c (°C)	Ref.
styrene	1.2×10^{-4}	benzene	—CH_2—CHPh—	110	[12]
α-methylstyrene	pure	—	—CH_2—CMePh—	61	[2]
	0.76	THF		0	[1, 13, 14]
methyl atropate	pure	—	—CH_2—C(COOMe)Ph—	− 8	[15]
	1.0	toluene		−40	[15]
formaldehyde	0.06	CH_2Cl_2	—O—CH_2—	30	[16]
acetaldehyde	pure	—	—O—CHMe—	−31	[17]
tetrahydrofuran	pure	—	—O—$(CH_2)_4$—	80	[18]
1,3-dioxolane	1.0	CH_2Cl_2	—O—CH_2—O—$(CH_2)_2$—	1	[19]
phthalaldehyde	1.0	CH_2Cl_2		−43	[20]
thioacetone	pure	—	—S—CMe_2—	95	[21]
n-hexyl isocyanate	2.0	DMF	—NHex^n—CO—	−22	[22]

[a] THF = tetrahydrofuran, DMF = dimethylformamide.

For a given medium and monomer concentration there is a particular ceiling temperature. Taking the reverse viewpoint one may say that for a particular temperature and medium there is a certain equilibrium monomer concentration. Thermodynamically there is no distinction; the only difference lies in the choice of independent variable. Experimentally both approaches may be used; in some cases it is feasible to allow the system to come to equilibrium at a particular temperature and then to measure the monomer concentration; in others, particularly where the equilibrium is less mobile, it is more convenient to plot the rate, yield, or degree of polymerization as a function of temperature, and to obtain the ceiling temperature by extrapolating the dependent variable to zero[24].

3. The Physical State of the System; Some Possible Situations

Since $\Delta G = 0$ at T_c it follows that

$$T_c = \Delta H / \Delta S \qquad (1)$$

where ΔH and ΔS are the appropriate heat and entropy changes for the polymerization process (per mol of monomer) under the prevailing conditions. Any factor which affects ΔG will also affect T_c, either through ΔH or ΔS or both. The main factors affecting ΔG for a given monomer are the concentration of monomer and the hydrostatic pressure. Minor factors are the nature of the solvent and the presence of dissolved solutes, particularly the polymer; or in the case where the polymer is insoluble, its degree of crystallinity. Any given situation may be analyzed in terms of a thermodynamic cycle containing the step:

$$M\,(liq) \rightarrow \frac{1}{n} M_n\,(amorphous) \qquad \Delta H_{lc}, \Delta S_{lc}, \Delta G_{lc}$$

This is illustrated for various particular cases below.

3.1. Polymer and Monomer Immiscible

This type of equilibrium polymerization is rather rare. It is characterized by a ceiling temperature below which there is *complete* conversion of monomer to polymer, just as a pure liquid freezes completely when the temperature is below its freezing point. *n*-Butyraldehyde may be an example of this[25].

If the polymer is formed in the crystalline state (at a temperature below its melting point) there is an additional driving force favoring polymerization; this is probably an important factor in the polymerization of 2-piperidone[26]. Conversely it is thermodynamically advantageous to start from monomer in the supercooled (glassy) state rather than the crystalline state and this could be of assistance when attempting to polymerize "difficult" monomers such as acetone[27].

Formaldehyde[28], chloral[29], fluoral[29], tetrahydrofuran[30], and 1,3-dioxolane[30] provide examples of direct equilibrium between monomer vapor and condensed polymer and in these systems the depolymerization process is akin to sublimation.

3.2. Polymer Soluble in Monomer

There are many examples of this type. In contrast to immiscible condensed systems (Section 3.1) polymerization below T_c stops short at a point which, to a good approximation, is independent of the molecular weight of the polymer. This is illustrated in Figure 1 for the cationic polymerization of tetrahydrofuran[18].

Thermodynamic analysis of such systems takes account of the effect of polymer on the chemical potential of the monomer and also of the variation of the chemical potential of the polymer with composition. Eq. (2) is the resulting expression under conditions of moderately large degree of polymerization and not too small volume fraction Φ_2 of the polymer. Φ_1 is the volume fraction of the monomer and χ the polymer-monomer interaction parameter, which commonly has a value of 0.3—0.5.

$$\Delta G_{lc}/RT = 1 + \ln\Phi_1 + \chi(\Phi_2 - \Phi_1) \qquad (2)$$

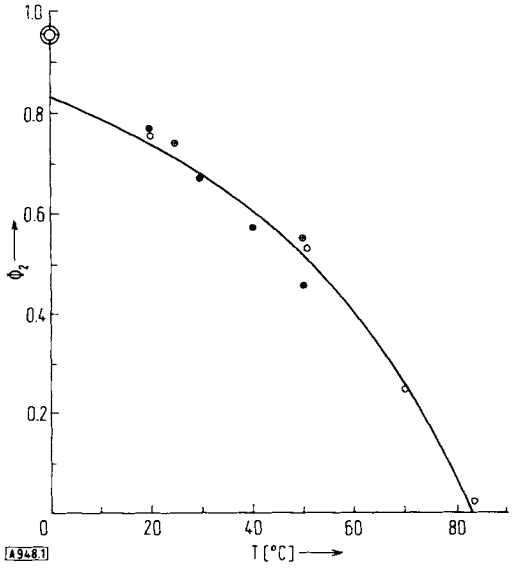


Fig. 1. Equilibrium volume fraction of polymer Φ_2 in the bulk polymerization of tetrahydrofuran [18]. The three sets of points (●, ○, ⊕) come from three different groups of workers. The line is drawn from eq. (2) taking $\chi = 0.3$, $\Delta H_{lc} = -12.4$ kJ mol^{-1}, $\Delta S_{lc} = -40.8$ J K^{-1} mol^{-1}.

This equation provides a satisfactory representation of the data for tetrahydrofuran (Fig. 1).

3.3. Polymer and Monomer in a Solvent

Numerous equilibrium systems of this type have been studied, some of which are shown in Table 1. Ceiling temperatures in such systems are usually quite sharp but the equilibrium monomer concentration $[M_e]$ varies with solvent and with polymer concentration. Thus for trioxane[31] at 30 °C, $[M_e]$ is 0.05 mol/l in benzene, 0.13 mol/l in 1,2-dichloroethane, and 0.19 mol/l in nitrobenzene. For α-methylstyrene[32] at 0 °C, $[M_e]$ is 0.78 mol/l if only a trace of polymer is present, but 0.34 mol/l in the presence of 4 mol/l of polymer (expressed in terms of mol monomer units).

The thermodynamic analysis of such systems involves the interaction between monomer and polymer (χ_{12}), solvent and polymer (χ_{32}), and monomer and solvent (χ_{13}). Eq. (3) is the resulting expression when the degree of polymerization is large, V_1 and V_3 being the molar volumes of monomer and solvent respectively[32].

$$\Delta G_{lc}/RT = 1 + \ln\Phi_1 + \chi_{12}(\Phi_2 - \Phi_1) + (\chi_{13} - \chi_{32}V_1/V_3)\Phi_3 \qquad (3)$$

Eq. (3) differs from eq. (2) by the inclusion of the last term. Generally χ_{13} shows a greater dependence on solvent than χ_{32} and is mainly responsible for the variation of $[M_e]$ or Φ_1 with solvent. When the variation of Φ_1 with Φ_2 is not too large it can be shown from eq. (3) that Φ_1 will be a linear function of Φ_2, as found for the polymerization of α-methylstyrene in tetrahydrofuran[32] and dioxane[33].

Any treatment in terms of eq. (3) is bound to be approximate since the interaction parameters are liable to vary with composition and temperature. Recourse has therefore frequently been made to a less exact treatment in terms of eq. (4),

$$T_c = \Delta H_{ss}/\Delta S_{ss} = \Delta H^0_{ss}/(\Delta S^0_{ss} + R\ln[M]) \qquad (4)$$

where ΔH_{ss} and ΔS_{ss} are the heat and entropy changes for the polymerization of monomer in solution to polymer in solution at the ceiling temperature for a monomer concentration [M]. Variations of the activity coefficients of the monomer and polymer with temperature or with composition are thus absorbed into the values of ΔH^0_{ss} and ΔS^0_{ss} (standard state 1 mol/l) instead of being expressed through the interaction terms in eq. (3). These usually show a sufficiently small and steady variation that eq. (4) provides a good representation of the experimental data, as shown for isobutyraldehyde[34] in Figure 2. The slope of the plot of log $[M_e]$ against T^{-1} gives an average value of ΔH^0_{ss} which may be combined with appropriate heats of solution of monomer and polymer to obtain ΔH_{lc}. Values of ΔH_{lc} or ΔH^0_{ss} obtained by the application of eqs. (2), (3), and (4) are generally in good agreement with calorimetric data. Details may be found in the Polymer Handbook[23].

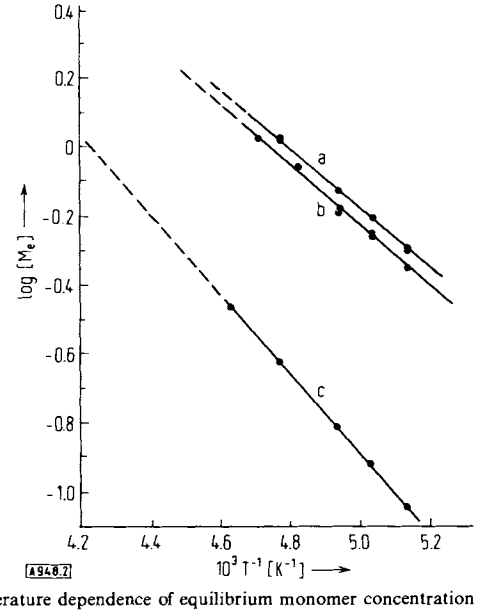


Fig. 2. Temperature dependence of equilibrium monomer concentration of isobutyraldehyde in: a, tetrahydrofuran; b, diethyl ether; and c, *n*-pentane [34].

Eq. (4) may also be derived from kinetic considerations, assuming that long chain polymer is formed[24]. The variation of $[M_e]$ with solvent and polymer concentration must reflect the variation of the propagation and depropagation rate constants with the nature of the reaction medium. For a given medium the ceiling temperature must of course be independent of the mechanism of the reaction, provided the polymer has the same structure.

3.4. Soluble Monomer and Insoluble Polymer

When a solution of monomer gives an insoluble polymer, it is possible for the crystallinity and hence the free energy of the polymer to vary with the solvent. An example is the formation of poly(3-methyl-1-butene sulfone) from mix-

tures of 3-methyl-1-butene and sulfur dioxide[35]. In sulfur-dioxide-rich mixtures the polymer has a free energy up to 3kJ mol^{-1} lower than that formed from a 3-methyl-1-butene-rich mixture at the same temperature and evidence has been obtained that the former polymer is more crystalline than the latter[36].

4. Effect of Pressure

The variation of T_c with pressure P may be expressed in the form of the Clapeyron-Clausius equation

$$d\ln T_c/dP = \Delta V/\Delta H \quad (5)$$

where ΔV and ΔH are the volume and enthalpy changes for the polymerization under the prevailing conditions. For pure α-methylstyrene[2,3] and for tetrahydrofuran[37] $\log T_c$ has been shown to be a linear function of pressure, the slope being consistent with the known values of ΔV and ΔH. Since practically all addition polymerizations are accompanied by a decrease in both volume and enthalpy the most favorable thermodynamic conditions for polymerization are high pressure and low temperature, a point worth bearing in mind when attempting to polymerize "difficult" monomers such as acetone. Generally one or other of these variables has been applied to encourage such monomers to polymerize, but seldom both together. The effect of pressure can be quite substantial, of the order of 100 K rise for a pressure of several thousand atmospheres.

5. Effect of Monomer Structure on Polymerizability

5.1. Compounds Containing Double Bonds (C=C, C=O, N=C)

Ethylene and most mono-substituted ethylenes can be readily polymerized and the back reaction is unimportant except for exceptionally low concentration and high temperature, for example at 10^{-3} mol/l and 120 °C for styrene. Reversibility is more in evidence for 1,1-disubstituted ethylenes and the ability of the monomer to polymerize is then critically dependent on the nature of the substituents, especially their bulkiness. This may be seen, for example, in the series CH_2=CRCOOMe. For R = Me (methyl methacrylate) the monomer polymerizes at 60 °C, but for R = Et, *n*-Pr, and Ph, the temperature must be lowered, say to −78 °C to bring about polymerization. For R = *iso*-Pr, *n*-Bu, *iso*-Bu, *sec*-Bu, *tert*-Bu, cyclohexyl, and benzyl high polymer cannot be made at any temperature[38,39]. Again, for the series CH_2=CMeX, the equilibrium concentration of monomer in tetrahydrofuran at 0 °C increases in the order β-naphthyl < *p*-biphenylyl < phenyl and polymerization does not occur for *o*-substituted aromatic substituents, including α-naphthyl[14,39,40]. In this series both ΔH^0_{ss} and ΔS^0_{ss} show variations with structure, but taking ethylenic monomers as a whole[24] ΔH is more sensitive to structure than ΔS.

Two effects on ΔH may be distinguished. First, resonance or hyperconjugation in the monomer tends to lower $-\Delta H$, some of the stabilization energy being lost on polymerization; second, steric hindrance in the polymer tends to lower $-\Delta H$. The first effect operates for styrene and the second for most 1,1-disubstituted ethylenes such as isobutene, methyl methacrylate, and α-methylstyrene.

Before leaving ethylenic monomers we may note that a methoxy group in place of a methyl group has a decidedly adverse effect on polymerizability. Thus α-methoxystyrene cannot be polymerized[4]. Conversely a nitrile group in place of an ester group has a beneficial effect: atroponitrile, CH_2=CPhCN, has a ceiling temperature much above that of methyl atropate[15,41].

Similar effects of substituents may be seen in the case of aldehydes. Thus formaldehyde is readily polymerized in solution if the concentration exceeds the equilibrium value[16] (0.06 mol/l in methylene chloride at 30 °C) but acetaldehyde and propionaldehyde must be cooled below −31 °C to induce them to polymerize in the pure state[17]. Further substitution in the α position to give isobutyraldehyde, Me_2CH—CHO, lowers T_c to −63 ° for a 1 M solution in tetrahydrofuran[34]. Pivalic aldehyde, Me_3C—CHO, is unpolymerizable at −78 °C[42]. Substitution by halogen, however, has a beneficial effect. Thus pure liquid 1,2-dichloropropionaldehyde, CH_2Cl—CHCl—CHO, has a ceiling temperature in the region of 0 °C[43]. The substituents have a considerable effect on both ΔH and ΔS in the polymerization of aldehydes.

Certain isocyanates polymerize through the N=C bond to give 1-nylons and a ceiling temperature effect is shown very clearly in the case of *n*-hexyl isocyanate[22] (Table 1). The non-polymerizability of many other isocyanates, particularly those substituted close to the nitrogen atom, is attributable to a lowering of the ceiling temperature. For example isopropyl[22] and 1-phenylethyl[44] isocyanates will not polymerize but phenyl[45] and 2-phenylpropyl[44] isocyanates will polymerize.

Many alkenes copolymerize with sulfur dioxide to give 1:1 copolymers (polysulfones) regardless of the composition of the feed and thermodynamically such systems may be treated like homopolymerizations. These reactions exhibit well-defined ceiling temperatures and were in fact the first in which the effect was recognized[9]. Increasing substitution by alkyl groups near the double bond causes a progressive lowering of ceiling temperature until with alkenes such as 2-ethyl-1-butene, 2,4,4-trimethyl-1-pentene, and 4-methyl-2-pentene no copolymer is formed at any temperature[46].

5.2. Ring Compounds

The compounds discussed in Section 5.1 may be regarded as two-membered rings. If the rings are enlarged by the incorporation of successive methylene groups we may expect the free energy of polymerization at first to become more negative, to be close to zero for five- and six-membered rings, then to become negative again and finally to approach a value close to zero. This statement is based on data for the cycloalkanes[24]. Alkyl substituents invariably make ΔG_{lc} less negative (more positive) and so reduce

Table 2. Polymerizability (+ or −) of some unsubstituted rings.

Group	Type of ring		Name of 5-ring	No. of ring members 5	6	7
1	1,3-C_nNO		2-oxazolidinone	−	+	
2	1,3-C_nN_2		2-imidazolidinone	+	−	+
3	1,2-C_nOS		1,2-oxathiolane 2,2-dioxide	+	−	
4	1,3-C_nO_2		1,3-dioxolane	+	−	+
5			ethylene carbonate	−	+	
6	1,2-C_nS_2		1,2-dithiolane	+	+	+
7	C_nN		pyrrolidine	−	−	+
8			2-pyrrolidinone	+	+	+
9			succinimide	−	−	
10			2-pyrrolidinethione	−		+
11	C_nO		tetrahydrofuran (oxolane)	+	−	+
12			2-oxolanone (γ-butyrolactone)	+	+	+
13			2,5-oxolanedione (succinic anhydride)	−	−	+
14	C_nS		2-thiolanone (γ-thiobutyrolactone)	−	+	+

the thermodynamic polymerizability, as for ethylene derivatives. But whereas the cycloalkanes are not generally polymerizable for kinetic reasons, heterocyclic compounds nearly always polymerize by ring-opening when it is thermodynamically possible; in other words non-polymerizability may nearly always be taken as synonymous with a positive free energy of polymerization.

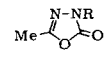
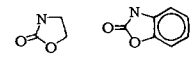
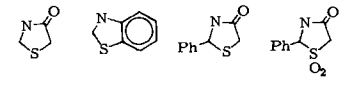
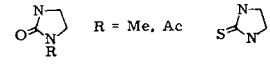
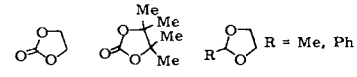
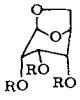
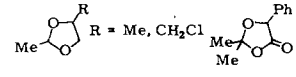
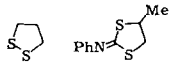
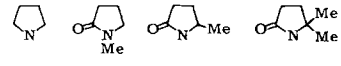
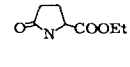
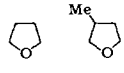
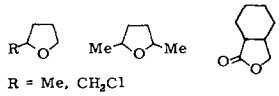
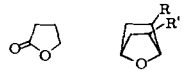
The polymerizability of fourteen different types of unsubstituted five-, six-, and seven-membered ring compounds is summarized in Table 2. It will be observed that seven-membered rings generally polymerize (there are some exceptions to this rule, not shown in Table 2), but that with five- and six-membered rings sometimes both polymerize (groups 6, 8, 12), sometimes neither polymerize (groups 7, 9, 13), sometimes only the five-membered rings polymerize (groups 2, 3, 4, 11) and sometimes only the six-membered rings polymerize (groups 1, 5, 14). This reflects the sensitivity of the sign of ΔG to small changes in the nature of the five- and six-membered rings.

As an example of the effect of substituents we show the behavior of five-membered rings in Table 3. A reaction of particular interest is the formation of polysaccharides from the bicyclic dioxolane derivatives[47, 48]. Details, and similar tables for six- and seven-membered rings, may be found elsewhere[16, 49].

6. Ring-Chain Equilibria Involving Rings of Different Sizes

When tetraoxocane, the cyclic tetramer of formaldehyde, is polymerized in 1,2-dichloroethane at 50 °C, its concentration falls to an equilibrium value of less than 0.008 mol/l, but at the same time an equilibrium concentration of 0.2 mol/l trioxane is built up[50]. Such behavior is typical of a whole range of cyclic compounds[23, 49]. The establishment of equilibrium between cyclic compounds containing different numbers of repeat units usually occurs *via* linear polymer or oligomer but sometimes a direct ring expansion mechanism is available as in the polymerization of cycloalkenes on the catalyst $WCl_4/ROH/RAlCl_2$ to give a macrocyclic polyene. For cyclooctene there is evidence for the

Table 3. Polymerizability of five-membered rings (hydrogen atoms not shown).

Ring	Polymerized	Not polymerized
C_2N_2O	[a]	 R = Me, Ph
C_3NO	R = Me, Ph etc. [b]	
C_3NS		
C_3N_2		 R = Me, Ac
C_3OS		
C_3O_2	R = H, Me, CH_2Cl, Ph	 R = Me, Ph
	 R = H, Me	 R = Me, CH_2Cl
C_3S_2		
C_4N		
		
		R = H, Me, nAm
C_4O		 R = Me, CH_2Cl
	 R = R' = H; R = *endo*-Me, R' = H; R = *exo*-Me, R' = H; R = *exo*-Me, R' = *endo*-Me	R = R' = *exo*-Me
C_4S		

[a] Polymer is $-[CO-NH-N(COMe)]-$.
[b] Polymer is $-[CH_2-CH_2-N(COR)]-$.

formation of a range of cyclic compounds containing up to 15 or more monomer units[51,52]. Likewise in the polymerization of tetrameric dimethylsiloxane, $(Me_2SiO)_4$, it has been established that the equilibrium mixture contains cyclic structures with up to 400 monomer units, the total macrocyclic population representing up to 10% of the whole polymer[53].

The data on the dimethylsiloxane system provided the first and still the most extensive test of the Jacobson-Stockmayer[54] theory of ring-chain equilibria. The theory assumes that the rings are strainless, that the end-to-end distances of linear chains are governed by Gaussian statistics (random-flight model, no excluded volume effect), that the probability of ring formation is governed by the frequency with which the ends of linear chains coincide, and that the probability of bond formation is independent of whether the two ends form part of the same or separate chains. The theory has recently been modified[55] to take account of valence angles and excluded volume effects (rotational isomeric states model) and in this modified form not only predicts that K_x for the equilibrium

$$\underset{\text{(linear)}}{M_y} \rightleftharpoons \underset{\text{(linear)}}{M_{y-x}} + \underset{\text{(cyclic)}}{c\text{-}M_x} \qquad K_x$$

is a linear function of $x^{-2.5}$, as found experimentally for $x > 15$, but also gives the correct value of the proportionality constant (Fig. 3). Deviations for $x < 15$ may be attributed to the failure of the assumption that the rings are strainless, *i.e.* for small rings the enthalpy of polymerization must also be taken into account.

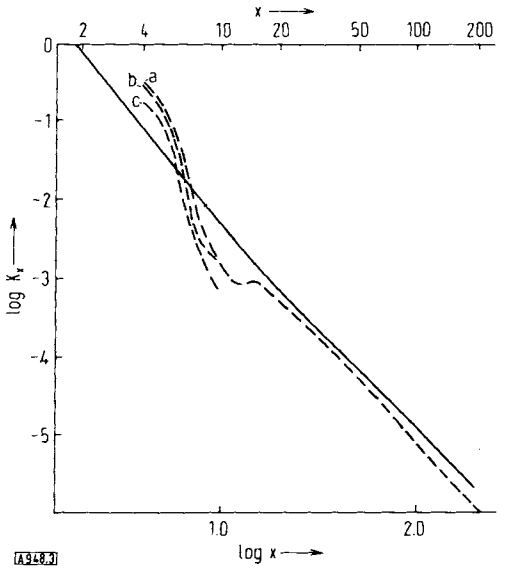


Fig. 3. Macrocyclic equilibrium constants for $(Me_2SiO)_x$.
$M_y \rightleftharpoons M_{y-x} + c\text{-}M_x$, K_x.
a, b, c are experimental curves of three groups of workers. Full line calculated by *Flory* and *Semlyen* [55].

7. Copolymerizations Involving Reversible Propagation

The copolymerization of two monomers M_1 and M_2 is generally considered in terms of four propagation steps:

$$M_1^* + M_1 \rightarrow M_1^* \quad k_{11} \qquad r_1 = \frac{k_{11}}{k_{12}}$$

$$M_1^* + M_2 \rightarrow M_2^* \quad k_{12}$$

$$M_2^* + M_2 \rightarrow M_2^* \quad k_{22} \qquad r^2 = \frac{k_{22}}{k_{21}}$$

$$M_2^* + M_1 \rightarrow M_1^* \quad k_{21}$$

where M_1^*, M_2^* represent growing polymer chains possessing M_1 and M_2 end-units respectively. The copolymer composition, expressed as the relative rates of removal of the two monomers, $d[M_1]/d[M_2]$, is then given by the Lewis-Mayo equation:

$$\frac{d[M_1]}{d[M_2]} = \frac{[M_1]}{[M_2]} \frac{\{r_1[M_1]+[M_2]\}}{\{r_2[M_2]+[M_1]\}} \tag{6}$$

This equation has been found satisfactory for a wide variety of monomers, but it is clear that it may fail if one of the reverse reactions becomes important compared with its forward reaction, as may happen when the temperature is close to the ceiling temperature for the homopolymerization of one of the monomers. If M_2 is far above its ceiling temperature then it may so happen that although $M_2^* + M_2 \rightarrow M_2^*$ is strongly reversed, $M_1^* + M_2 \rightarrow M_2^*$ is not. Under these circumstances the *effective* values (not the actual values) of k_{22} and r_2 are zero and eq. (6) reduces to eq. (7):

$$\frac{d[M_1]}{d[M_2]} = 1 + r_1 \frac{[M_1]}{[M_2]} \tag{7}$$

Figure 4 shows an example of this type of behavior for M_2 = α-methoxystyrene, a monomer which itself is unpolymerizable[4]. At low values of $[M_1]/[M_2]$ the copolymer tends to the alternating 1:1 composition. If r_1 is less than 0.01 for this type of system the composition of the copolymer will be close to 1:1 over a wide range of feed composition, as for example in the radical copolymerization of styrene with *trans*-1,2-dibenzoylethylene[56]. Other unpolymerizable monomers which can be copolymerized with a second monomer to give compositions close to 1:1 include oxygen, carbon monoxide and dioxide, carbon oxide sulfide and disulfide, sulfur dioxide, phenyl isothiocyanate, tetrahydropyran, 2-methyltetrahydrofuran, benzaldehyde, hexafluoroacetone, 1,1-diphenylethylene, *trans*-stilbene, *trans*-1,2-di(2-pyridyl)ethylene, *trans*-1,2-diacetylethylene, and α-stilbazole. Details are given elsewhere[49].

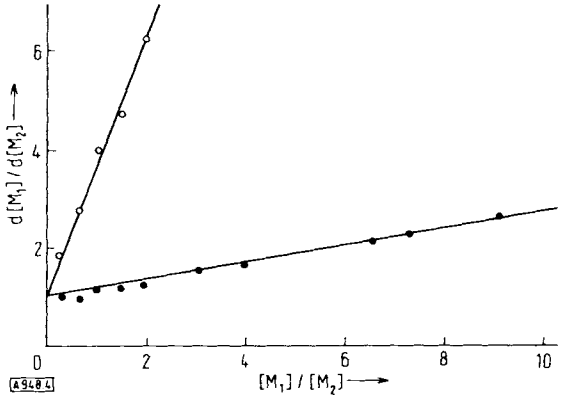


Fig. 4. Radical copolymerization of α-methoxystyrene (M_2) with methyl acrylate (—•—•—) and methyl methacrylate (—o—o—) at 60 °C [4]. $r_1 = 0.17$ for methyl acrylate; $r_1 = 2.5$ for methyl methacrylate.

The limiting composition at high temperature and low $[M_1]/[M_2]$ for copolymerization systems containing reversible propagation steps involving M_2 is not always 1:1. Sometimes only homopolymer of M_1 is produced, indicating that both $M_2 + M_2^* \rightarrow M_2^*$ and $M_1^* + M_2 \rightarrow M_2^*$ are strongly reversed; this behavior is found with the copolymerization of two alkenes with sulfur dioxide[57]. In other cases the limiting composition is 1:2 ($M_1 : M_2$) indicating that M_2 can add to $M_1M_2^*$ but not to $M_1M_2M_2^*$; this applies for example to the radical copolymerization of styrene[58,59], methyl acrylate[58], and acrylonitrile[58] (M_1) with methyl atropate (M_2) at 60 °C.

The reason for these different types of behavior must be sought in the reasons for the reversibility or non-occurrence of the polymerization of M_2. If the heat of polymerization of M_2, and hence ceiling temperature, is low because of

steric strain in the polymer it is likely that this strain will be entirely removed if every other M_2 unit is replaced by an M_1 unit. Sometimes this will be so if every third M_2 unit is replaced by M_1. These two cases correspond to the limiting compositions of 1:1 and 1:2 ($M_1:M_2$), examples of which have been given above. If, however, the heat of polymerization of M_2 is low for other reasons, there may be no significant difference in the heats, and hence reversibilities, of the reactions $M_1^* + M_2 \rightarrow M_1M_2^*$ and $M_2^* + M_2 \rightarrow M_2M_2^*$. In this case only homopolymer of M_1 will be produced under conditions of high temperature and low $[M_1]/[M_2]$.

A number of papers have been published[57, 60, 61] concerning the theoretical description of the transition from "normal" behavior as described by eq. (6) to "limiting" behavior, for example as described by eq. (7), but so far there have been comparatively few experimental studies[57, 62–65].

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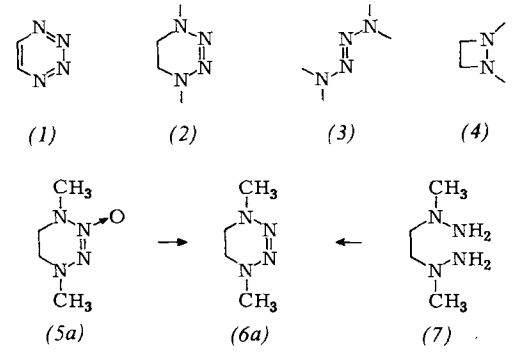
Isolation and Identification of v-Tetrazine Derivatives on Decomposition of Nitrosamine Anions[**]

By *Dieter Seebach, Dieter Enders, Bernd Renger,* and *Werner Brügel*[*]

Dedicated to Professor F. Kröhnke on the occasion of his 70th birthday

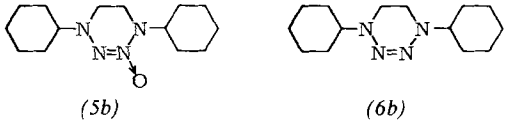
Hitherto there has been no compound with an established *v*-tetrazine structure[1] in which four contiguous nitrogen atoms are incorporated into an aromatic *(1)*, partially [*e.g. (2)*] or fully hydrogenated six-membered ring; tetrahydro derivatives *(2)* would be particularly interesting for comparison with the well known, open-chain 2-tetrazenes *(3)* of *trans* configuration, as possible inverse dienophiles, and as precursors for preparation of diazetidines *(4)*.

We have now found that the *N*-oxides *(5a)*, *(5b)*, and *(5c)*, respectively, can be isolated as decomposition products of metalated nitrosamines[2] (dimethylnitrosamine, methylcyclohexylnitrosamine, and 1-nitrosopiperidine) in 30%—45% yields and can be reduced quantitatively by trimethyl phosphite to the oxygen-free compounds *(6a)*, *(6b)*, and *(6c)*, respectively. Proof of the structures of the new compounds (C, H, and N contents within 0.3%, osmometric molecular weights within 5% of the theoretical values) rests on spectroscopic studies: The mass spectra of *(5a)*—*(5c)* show an $(M-O)$, and *(6c)* an $(M-N_2)$ line. In the NMR spectrum ($CDCl_3$) the presence, for example, of C_s symmetry only in *(5a)* is evident from the appearance of two CH_3 singlets ($\delta=2.92$ and 3.08 ppm) and an AA'BB' multiplet (3.3 ppm) for the CH_2 groups, whilst *(6a)* shows a 6H (3.05 ppm) and a 4H singlet (3.12 ppm). In the UV region (CH_3OH) *(5a)*—*(5c)* have $\lambda_{max}=288$—294 nm ($\log\varepsilon\approx 4.08$), and the tetrahydro-*v*-tetrazines *(6a)*—*(6c)*, like 2-tetrazenes *(3)*, have two maxima [270—280 ($\log\varepsilon\approx 3.7$) and 220—225 nm ($\log\varepsilon\approx 3.4$)]. The IR spectra contain intense bands in the region characteristic for azoxy (1480 and 1300 cm^{-1}) and azo compounds (1450 cm^{-1}). In the N1s-ESCA spectrum of *(5c)* the ionization typical[3] of azoxy-N atoms is present at 403 eV, whereas the reduced *(6c)* shows only a relatively sharp band at 399 eV. Finally, *Nelsen* and *Fibinger*[4] obtained *(6a)* independently in 4% yield by oxidation of the bishydrazine *(7)*, and the two samples were identical.

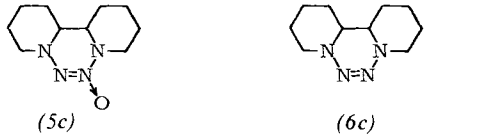


(1) *(2)* *(3)* *(4)*

(5a) *(6a)* *(7)*



(5b) *(6b)*



(5c) *(6c)*

(5a), m. p. 59.5—60.0 °C
(5b), m. p. 83.0—84.5 °C
(5c), m. p. 79.5 °C

(6a), b. p. 85 °C/10 torr
(6b), dec. 92—94 °C
(6c), m. p. 67 °C

The route by which the oxides *(5)* are formed from the nitrosamines is at present under study; above −80 °C the solutions of the lithium derivatives[2] give intense ESR signals. Hence we are certain that decomposition occurs by way of radicals.

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[1] This structure has been disproved for many of the compounds that were considered to be *v*-tetrazines in the earlier literature [*V. P. Wystrach*, Heterocycl. Compounds *8*, 106 (1967)]. We thank Prof. Dr. *S. Hünig*, Prof. Dr. *A. R. Katritzky*, and Dr. *V. P. Wystrach* for pertinent information.

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8-Quinolinecarboxylic Acid from 3,1-Benzoxazin-4-ones and Enamines

By *Wolfgang Steglich* and *Oswald Hollitzer*[*]

3,1-Benzoxazin-4-ones and ynamines afford 4-(dialkylamino)quinolines and 3,3-disubstituted 4(3*H*)-quinolones[1]. With enamines the reaction takes a different course: the CO_2 group is retained and 8-quinolinecarboxylic acids such as *(3)* and *(4)* are formed.

If the 2-(trifluoromethyl)-3,1-benzoxazin-4-ones *(1a)* to *(1c)*[1] are treated in ether or acetonitrile with *N,N*-diethyl-1-butenamine, the diethylammonium salts *(2)* of the 8-quinolinecarboxylic acids are precipitated after a short time; these salts are filtered off and partitioned between 1 N NaOH and ether, the free acids *(3)* being obtained by acidifying the aqueous phase. The mother liquor remaining after isolation of *(2)* contains varying amounts of the diethylamides *(5)* of *N*-(trifluoroacetyl)anthranilic

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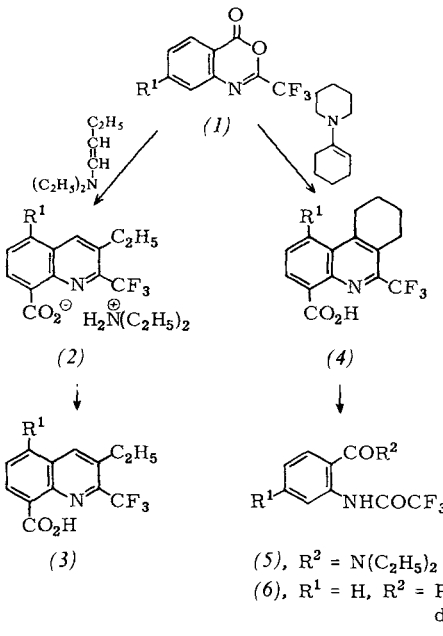


(1)

(2)

(3)

(4)

(5), $R^2 = N(C_2H_5)_2$

(6), R^1 = H, R^2 = Piperidino

ingly soluble acid can be obtained pure by crystallization from $CHCl_3$.

The structures of compounds *(3)* and *(4)* follow unambiguously from the analytical and spectroscopic data and, in the case of *(3a)*, was confirmed by degradation to the known 2-(trifluoromethyl)quinoline[3].

As in the ynamine reaction[1], the formation of the quinolinecarboxylic acids *(3)* and *(4)* is initiated by attack of the nucleophile on the C=N double bond, but in the present case the resulting betaine *(7)* can, after ring-opening, be converted by a proton shift into a phenylazabutadiene *(9)* which affords the products on disrotatory 6π-ring closure and ejection of amine[4].

This differs from other reactions of similar type[5,6] in that the quinoline system is rapidly produced, even on ice-cooling, probably due to conjunction of several factors. It is conceivable that in the transformation *(7)*→*(8)* the resulting carboxylate group favors formation of the (*E*)-configuration that is necessary for the electrocyclic ring closure and that the ring closure is assisted by hydrogen bonding and the influence of the CF_3 group[7].

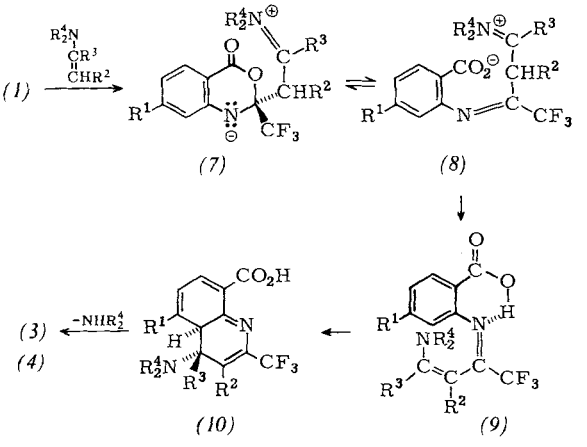
Table 1. Properties of the 8-quinolinecarboxylic acids *(3)* and *(4)*.

Cpd. [a]	R^1	Yield (%) [b]	M. p. [°C]	^{1}H-NMR [2] 4-H	5-H	6-H	7-H	
(3a)	H	65 [c]	199–200 $CHCl_3$	9.44 (s) CF_3CO_2H	8.67 (dd)	8.22 (dd)	9.11 (dd)	$J_{5,6}$ = 8.5 Hz $J_{5,7}$ = 1.5 Hz $J_{6,7}$ = 7.0 Hz
(3b)	Cl	48 [c]	146–147 $CHCl_3$, pet. ether	8.93 (s) $CDCl_3$		8.02 (d)	8.85 (d)	$J_{6,7}$ = 8.0 Hz
(3c)	NO_2	67 [d]	139 CCl_4	9.27 (s) $CDCl_3$		8.62 (d)	8.94 (d)	$J_{6,7}$ = 8.0 Hz
(4)	H	48 [d, e]	239.5–240.5 $CHCl_3$	--	8.62 (dd) $CDCl_3$	8.12 (dd)	9.12 (dd)	$J_{5,6}$ = 8.5 Hz $J_{5,7}$ = 1.5 Hz $J_{6,7}$ = 7.0 Hz

[a] Satisfactory analyses were obtained for all the compounds isolated.
[b] *(3a)*—*(3c)*: yields of ammonium salt without work-up of the mother liquor.
[c] In acetonitrile.
[d] In ether.
[e] With 22% of *(6)*.

acid. Like *(3)* these amides are soluble in sodium hydroxide solution but can, if required, be separated by virtue of their insolubility in aqueous sodium hydrogen carbonate.

Treatment of *(1a)* with 1-cyclohexenylpiperidine yields a mixture of 7,8,9,10-tetrahydro-4-phenanthridinecarboxylic acid *(4)* and the piperidide *(6)* (m. p. 141 °C) of *N*-(trifluoroacetyl)anthranilic acid, from which the more spar-



(7)

(8)

(9)

(10)

3-Ethyl-5-nitro-2-(trifluoromethyl)-8-quinolinecarboxylic acid (3c)

A stirred suspension of the benzoxazinone *(1c)* (2.6 g) in anhydrous ether (15 ml) is treated dropwise with *N*,*N*-diethyl-1-butenamine (1.27 g) in ether (3 ml). After overnight stirring, the salt *(2c)* is filtered off (yield 2.6 g, 67%; m. p. 161—165 °C). The free acid *(3c)* is obtained by partitioning the salt between ether and 1 N NaOH, acidifying the aqueous phase, and recrystallizing the precipitate from CCl_4; yield 1.9 g, 60%.

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[2] All the chemical shifts δ are in ppm relative to TMS (δ = 0.00).

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[4] In the intermediate *(9)*, $R^2 + R^3 = -(CH_2)_4-$, arising from *(1)* and cyclohexenylpiperidine the terminal double bond is necessarily (*Z*)-configurated. Thus, at least in this case, the aromatic compound is formed by *syn*-elimination of amine.

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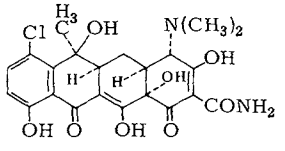
[7] Compare the acceleration of the Claisen rearrangement by negative substituents: *C. G. Krespan*, Tetrahedron *23*, 4243 (1967).

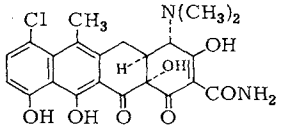
Total Synthesis of Anhydroaureomycin[**]

By *Hans Muxfeldt*, *Heinrike Döpp*, *John E. Kaufman*, *Joachim Schneider*, *Philip E. Hansen*, *Andrew Sasaki*, and *Timothy Geiser*[*]

Anhydroaureomycin *(2)*, which is readily accessible from aureomycin *(1)*[1] by treatment with mineral acids[2], can



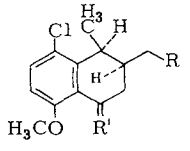
(1)

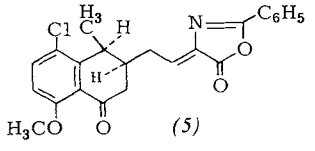


(2)

be reconverted into aureomycin *(1)* by a remarkable photooxidation and subsequent reduction[3]. Thus, a total synthesis of *(1)* can be limited to a total synthesis of *(2)*.

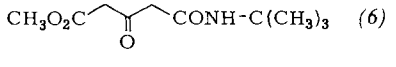
Reduction of the racemic nitrile *(3)*[4] by hydridodiisopropylaluminum and subsequent acid work-up affords the aldehyde *(4)* (m. p. 120—124 °C) which undergoes condensation with hippuric acid and lead acetate in acetic anhydride to yield the oxazolone *(5)* [m. p. 157—159 °C; UV (acetonitrile): $\lambda_{max}(\varepsilon)=222$ (33300), 242 (16600), 255 (10300), and 299 nm (26100)].





(5)

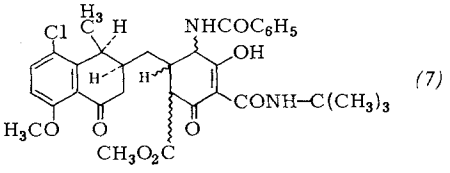
(3), R = CN, R' = $-O-CH_2-CH_2-O-$
(4), R = CHO, R' = O



(6)

A further structural unit used was the methyl *N-tert*-butyl-3-oxoglutaramate *(6)*; this compound was obtained (m. p. 65—66 °C) from dimethyl 3-oxoglutarate with *tert*-butylamine and *p*-toluenesulfonic acid in boiling dioxane.

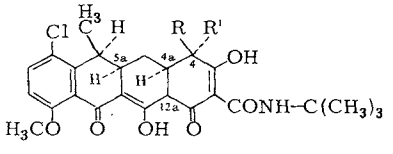
Addition of *(5)* and *(6)* to a boiling mixture of tetrahydrofuran and ether containing one equivalent of sodium hydride yields, analogously to reactions described previously[5], a mixture of stereoisomers and tautomers *(7)*. The structure of this mixture follows from analytical data, the IR spectrum ($\lambda_{max}=3.30$, 5.71, 5.95, and 6.30 µm in $CHCl_3$) and the UV spectrum [$\lambda_{max}(\varepsilon)=227$ (31400), 278 (16000), and 326 nm (3700) in 0.01 N methanolic NaOH].



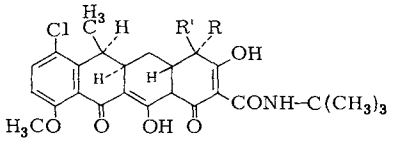
(7)

When an excess of sodium hydride is used for a reaction time of 48 h, further condensation of the intermediate compounds *(7)* affords a 76% yield of a stereoisomeric and tautomeric mixture of the tetracyclic compounds *(8)*, *(9)*, *(10)*, and *(11)*. That these are tetracyclic products follows from the analytical data of the mixture and its characteristic absorption [λ_{max} in methanolic sodium borate solution at 462 nm ($\varepsilon=50000$), absorption of fully conjugated borate complexes]. All four isomers could be isolated pure by crystallization and chromatography and then characterized. An appreciably easier isolation of *(9)* and *(11)* was achieved on finding that *(8)* epimerized to *(9)*, and *(10)* to *(11)*, on dissolution in pyridine under nitrogen. The mixture of *(9)* and *(11)* was readily separated by crystallization and subsequent chromatography of the mother liquors on silica gel.

A good indication of the configuration at C-4a in *(8)* and *(9)*, and also in *(10)* and *(11)*, was provided by the electronic spectra of these compounds in 0.01 N methanolic sodium hydroxide. In alkaline solution, *(8)* and *(9)* can pass into a coplanar, torsion-free, fully conjugated



(8), R = $NHCOC_6H_5$, R' = H
(9), R = H, R' = $NHCOC_6H_5$



(10), R = $NHCOC_6H_5$, R' = H
(11), R = H, R' = $NHCOC_6H_5$

anion by enolization, but in *(10)* and *(11)* C-12a remains tetrahedral because complete conjugation involves torsional strain (Fig. 1).

Further, an optically active compound (+)-*(12)* that is analogous to *(11)* in the configuration of its ring system

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[**] Tetracyclines, Part 8. — Part 7: *H. Muxfeldt, G. Hardtmann, E. Vedejs, F. Kathwala*, and *J. B. Mooberry*, J. Amer. Chem. Soc. *90*, 6534 (1968). This work was carried out at the University of Wisconsin, Madison, Wis., at Cornell University, Ithaca, N.Y., and at Universität Stuttgart. Financial support from the National Institutes of Health, the National Science Foundation, the Hoffman La Roche Anniversary Foundation, Chas. Pfizer & Co., Inc., and the Deutscher Akademischer Austauschdienst is gratefully acknowledged.

gives a CD spectrum differing unambiguously from that of (−)-6-demethyl-6-deoxytetracycline *(13)*[6].

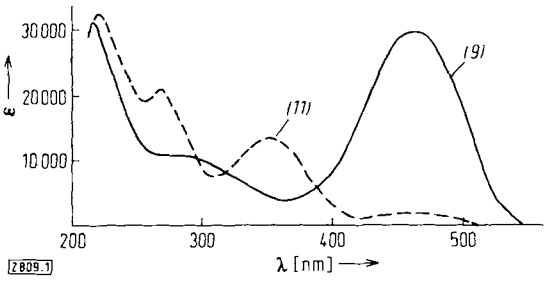
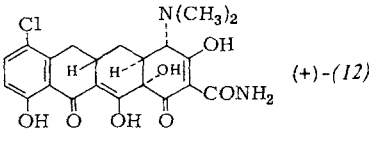
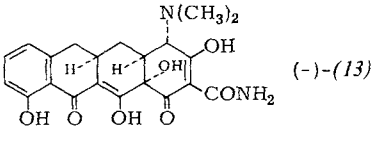


Fig. 1. Electronic spectra of *(9)* and *(11)* in 0.01 N methanolic NaOH.

Information about the configuration at C-4 in *(8)* and *(11)* is provided by the ^{1}H-NMR spectra. *(10)*, 4-H in $CDCl_3$: $\tau = 4.5$ (q), $J = 4$ Hz and in CF_3COOD: $\tau = 4.6$ (d), $J = 4$ Hz; *(11)*, 4-H in CF_3COOD: $\tau = 5.2$ (d), $J = 12$ Hz. These results show that in *(10)* 4-H and 4a-H must be equatorial and in *(11)* *trans*-diaxial. *(8)* and *(9)* behave analogously to *(10)* and *(11)*, respectively. Thus both *(9)* and *(11)* can be converted into anhydroaureomycin, but here we shall describe only the reactions leading from *(11)* to *(2)*.

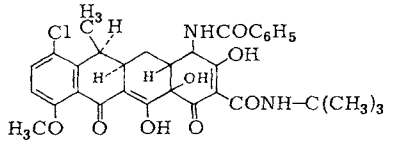


(+)-*(12)*

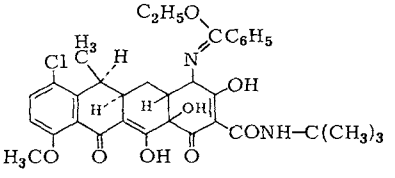


(−)-*(13)*

For *cis*-hydroxylation[7] on C-12a, oxygen was passed through a glass frit into a vigorously stirred solution of *(11)* in dimethylformamide and triethyl phosphite at −9 °C. After a few minutes 1.2 equivalents of potassium *tert*-butoxide was added and the whole was treated with oxygen for a further 20 min. On acidic work-up, a 76% yield of *(14)* was isolated and characterized by its ^{1}H-NMR spectrum and the UV spectra at various pH's that were typical of 12a-*cis*-hydroxylated compounds. ^{1}H-NMR spectrum: 4-H in $CDCl_3$, pyridine and D_2O: $\tau = 4.95$ (d), $J = 11.5$ Hz. UV spectrum in 0.1 M methanolic sodium borate solution: $\lambda_{max}(\varepsilon) = 218$ (30500), 269 (17200), and 338 nm (12750); in 0.01 N methanolic HCl: 220 (29700), 268 (23750), and 356 nm (15100); in 0.01 N methanolic NaOH: 218 (29000), 268 (19150), and 367 nm (9140).



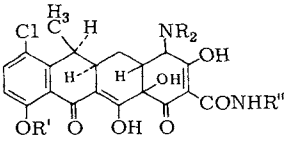
(14)



(15)

Fission of the amide group on C-4 of *(14)* by alkylation with *Meerwein*'s reagent[8] and subsequent hydrolysis of the benzimidate *(15)* by dilute HCl under the usual conditions proved very unsatisfactory; on the one hand, the tetrafluoroboric acid present prevented complete alkylation of *(14)* and on the other there occurred a partial acid-catalyzed epimerization of *(15)*; and finally the hydrolysis of *(15)* was not homogeneous. Only poor yields of the amine *(16)* and its C-4 epimer resulted, while fission back to the amides predominated.

The following method gave approximately quantitative yields of *(16)*:*(14)* was alkylated with *ca.* 5 equivalents of *Meerwein*'s reagent at room temperature in methylene chloride containing an excess of tetra-*N*-methyl-1,8-naphthalenediamine[9], the base then being precipitated as sparingly soluble tetrafluoroborate. After the alkylation the reaction mixture was treated with anhydrous methanol and worked up after a few hours. Naturally, none of the amide *(14)* is formed under these conditions and, further, epimerization of *(15)* is hindered in the acid-free medium[10]. *(16)* can be isolated easily as its crystalline tetrafluoroborate salt, from which it is liberated by sodium



(16), R = H, R' = CH_3, R'' = $C(CH_3)_3$
(17), R = R' = CH_3, R'' = $C(CH_3)_3$
(18), R = CH_3, R' = R'' = H

acetate. The configuration on C-4 of *(16)* follows from that of the reaction products. Mass spectrum of *(16)*: $m/e = 504$ (M).

Methylation of the 4-amino group by the usual alkylation agents such as methyl iodide affords only mixtures of *N*-mono-, *N*,*N*-di-, and *N*,*N*,*N*-tri-methyl derivatives which are difficult to separate, but *(17)* is obtained in good yield when *(16)* is treated with sodium trihydridocyanoborate[11] in the presence of an excess of *Hünig*'s base and formaldehyde. Acidic work-up affords the crystalline hydrochloride of *(17)*. Mass spectrum of *(17)*: $m/e = 532$ (M).

The protecting groups R' and R'' in *(17)* were removed by merely heating the compound in 48% HBr at 100 °C; during evaporation the hydrobromide of *(18)* crystallized from the reaction mixture. Mass spectrum of *(18)*: $m/e = 462$ (M). Electronic spectra in 0.1 M methanolic sodium borate solution: $\lambda_{max}(\varepsilon) = 220$ (13900), 244 (15800), 268 (12500), and 384 nm (16240); in 0.01 N methanolic NaOH: 228 (13800), 244 (15600), 264 (13600), and 386 nm (14900); in 0.01 N methanolic HCl: 231 (14300), 268 (17000), 347 (11800), and 368 nm (11800). The absorption at $\tau = 5.98$ in the ^{1}H-NMR spectrum is characteristic of *trans*-4-H/4a-H in tetracyclines[12].

(18) is spontaneously dehydrated by dichlorodicyanobenzoquinone in dioxane[13]. The dehydration product is identical with anhydroaureomycin *(2)* in its chromatographic behavior on polyamide and distinctly different from the 4-*epi*-isomer. IR, electronic, mass, and ^{1}H-NMR spectra are also identical. Electronic spectrum in 0.01 N HCl:

$\lambda_{max}(\varepsilon)=228$ (28600), 274 (50000), 337 (4300), and 435 nm (8300). ^{1}H-NMR spectrum (100 MHz) in CF_3COOD: $\tau=7.32$ (s) C-6-methyl, 6.72 (s) *N*-methyl, 6.65 (s) *N*-methyl, 5.83 (d) 4-H ($J=2$ Hz)[12]. Mass spectrum: $m/e=460$ (M).

The low coupling constant of 4-H in the ^{1}H-NMR spectrum of *(2)* (whether obtained from natural or synthetic material) leads to the conclusion that *(2)* exists in a conformation in which the dihedral angle between 4-H and 4a-H lies between 65 and 105°, possibly owing to H-bonding between the nitrogen on C-4 and the OH group on C-12a.

This procedure may be regarded as a total synthesis of aureomycin *(1)* if the synthetic racemate of *(2)* can be resolved, which may be difficult because of ready epimerization at C-4.

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German version: Angew. Chem. *85*, 508 (1973)

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Structural Investigations of Tellurium Subhalides: Modified Tellurium Structures

By *Rüdiger Kniep, Dietrich Mootz,* and *Albrecht Rabenau*[*]

Dedicated to Professor Georg Brauer on the occasion of his 65th birthday

Only recently has the existence of tellurium subhalides Te_yX (X = Cl, Br, or I; $y \geq 1$) been unambiguously proved[1]. We report the first investigations of the structures of these compounds. They are intended to provide information as to how the "unsaturation" with respect to tellurium is reflected in the crystal structures.

We have further prepared the compounds Te_2Cl and Te_2I[2] as additions to those reported in [1]. Single crystals of all the compounds, suitable for structure analysis, were prepared. Their lattice constants were determined by angle measurements on a diffractometer or refined from previous data[1]; the values for Te_2Cl were determined photographically. The space groups were deduced from Weissenberg photographs. The unit cell of Te_3Cl_2 was transformed in order to achieve a monoclinic angle closer to 90°.

Table 1. Tellurium subhalides: crystallographic data.

	a / α	*b* / β	*c* [Å] / γ	Space group	*Z*
Te_3Cl_2	10.137	8.651	7.075	$P2_1/n$	4
	—	100.86°	—		
Te_2Cl	14.82	12.81	4.00	Pnam	8
Te_2Br	14.922	12.842	4.004	Pnam	8
Te_2I	15.294	13.694	4.123	Pnam	8
TeI	9.957	7.991	8.214	P1, P$\bar{1}$	8
	104.38°	90.13	102.91°		
Te_xI	15.384	4.179	12.001	C2, Cm	16
	—	128.09°	—	C2/m	atoms

As shown in Table 1, the subhalides of general composition Te_2X form an isotypic series. An orthorhombic structure had been reported for a 1:1 compound in the system tellurium-iodine[3]; however, the sample in question was probably triclinic TeI (see Table 1), as suggested by its orthorhombic pseudosymmetry, reinforced by frequent twinning, and a great similarity in lattice dimensions.

For the crystal structure analysis of Te_3Cl_2 we determined the intensities of 2610 independent reflections with $Mo_{K\alpha}$ radiation ($\theta_{max}=35°$) on an automatic single-crystal diffractometer; the *R* factor is at present 9.2% with corrections for absorption and extinction not being applied.

Figure 1 shows the building unit of this structure, an infinite tellurium screw, such as is present with a simpler conformation and higher symmetry in elemental tellurium. Each third Te atom binds two Cl atoms axially, thereby giving the composition Te_3Cl_2. The coordination of this

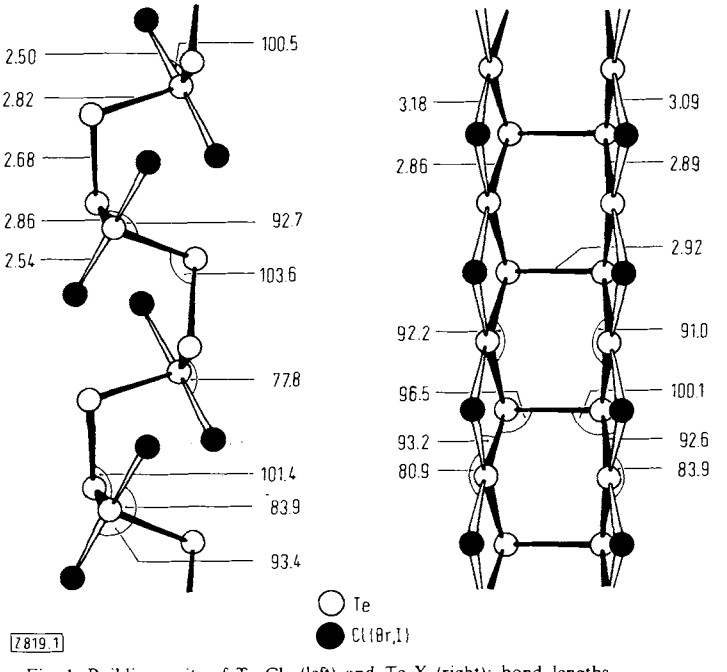

Fig. 1. Building units of Te_3Cl_2 (left) and Te_2X (right); bond lengths [Å] and bond angles [ ]. The data for Te_2X are those for Te_2I.

Te atom is trigonal-bipyramidal when the remaining lone pair is taken into account; analogous coordination of tellurium has been reported for, *e.g.*, the eight-membered rings of Cl_2TeS_7 and Br_2TeS_7[4]. The bond lengths and

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angles between Te atoms are similar to those in elemental tellurium. The shortest atom separations between neighboring building units are 3.4 Å.

Structure analyses for the isotypic halides Te_2X were carried out with Te_2Br and Te_2I. 748 reflections for the bromide ($\theta_{max}=25°$) and 1255 reflections for the iodide ($\theta_{max}=30°$) were measured with $Mo_{K\alpha}$ radiation on a diffractometer; the R factors were 7.5% and 8.1%, respectively, after anisotropic refinement. The data for the iodide were corrected for absorption.

Figure 1 also shows the macromolecular structural unit of this structure type. Here too a skeleton of Te atoms lies parallel to the crystallographic c-axis, this time with bridging halogen atoms on the edges[5]. All the atoms are in mirror planes perpendicular to the c-axis. The two Te atoms with bonds to halogen atoms show planar, approximately square coordination; this, and bivalent halogen atoms, were also found for the $(TeBr)_2$ four-membered ring of an N,N'-ethylenethiourea-$TeBr_2$ complex[7]. The two remaining independent Te atoms of the building unit are bonded only to tellurium in a trigonal-pyramidal arrangement.

Their relation to the structure of the semiconducting element makes the tellurium halides[8] a compound class that also has physical interest.

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[8] The structures of Te_xI and TeI are still under investigation. The intensities have also been measured on a diffractometer.

Reactions of Hexachlorodisilane with Methylene and Dichlorocarbene[**]

By *Manfred Weidenbruch* and *Claude Pierrard*[*]

During investigation of the chemical and thermal behavior of systems containing silicon-silicon bonds we have found that hexachlorodisilane *(1)* reacts smoothly with the dichlorocarbene generator phenyl(trichloromethyl)mercury[1] in the presence of sodium iodide[2] to yield pentachloro(trichloromethyl)disilane *(2)*:

$$\underset{(1)}{Cl_3Si{-}SiCl_3} + C_6H_5{-}Hg{-}CCl_3 \longrightarrow \underset{(2)}{Cl_3C{-}\overset{Cl}{\underset{Cl}{Si}}{-}SiCl_3} + C_6H_5HgCl$$

The molecular ion does not appear in the mass spectrum of *(2)* determined with 70 eV excitation energy, an effect observed also for other polyhalodisilanes, being replaced by a fragment poorer by one Cl atom, namely $Si_2CCl_7^+$ (m/e for $^{35}Cl=313$), along with the ions $Si_2Cl_5^+$, $SiCCl_5^+$, $SiCCl_4^+$, $SiCCl_3^+$, $SiCl_3^+$, CCl_3^+, $SiCl_2^+$, and CCl_2^+.

The reaction is remarkable insofar as no insertion of halocarbenes into Si—Cl bonds had been achieved previously[3]. The CCl_2-transfer is proved by the reaction of *(1)* with (bromodichloromethyl)phenylmercury[1-4] carried out under the same conditions since here too we were able to isolate only *(2)* and not the possible transmetalation product (bromodichloromethyl)pentachlorodisilane.

$$(1) + C_6H_5{-}Hg{-}CCl_2Br \longrightarrow (2) + C_6H_5HgBr$$

Reaction of *(1)* with sodium trichloroacetate, which has also been proposed as a source of dichlorocarbene[5], in tetrachloroethane to aid dissolution affords only a mixture of chloro(trichloroacetoxy)disilanes. Carrying out this reaction without a solvent, in a boiling excess of *(1)*, leads to pyrolysis and rearrangement that provide linear perchloropolysiloxanes *(3)* of which the members with $n=1$ [b.p. ≈ 50 °C/0.8 torr, mass spectrum: $m/e=361$ ($Si_3{}^{35}Cl_7O_2^+$) along with $Si_2Cl_5O^+$, $Si_2Cl_4O^+$, $Si_2Cl_3O^+$, $SiCl_3^+$] and $n=3$ [b.p. ≈ 100 °C/0.5 torr, mass spectrum: $m/e=589$ ($Si_5{}^{35}Cl_{11}O_4^+$) along with $Si_4Cl_9O_3^+$, $Si_3Cl_7O_2^+$, $Si_2Cl_5O^+$], predominate.

$$(1) + n\ NaO_2C{-}CCl_3 \xrightarrow{C_2H_2Cl_4} \begin{cases} Si_2(O_2C{-}CCl_3)_nCl_{6-n} + n\ NaCl \\ Cl_3Si(OSiCl_2)_nOSiCl_3 \quad (3) \end{cases}$$

Methylene, formed under Cu-catalysis from diazomethane *(4)*, reacts with *(1)* in ether between −40 and −30 °C to afford pentachloro(chloromethyl)disilane *(5)*, b.p. 20 to 25 °C/0.5 torr, which can be separated from unchanged *(1)* only with difficulty because of their similar volatilities; mass spectrum: $m/e=245$ ($Si_2CH_2{}^{35}Cl_5^+$).

On reaction with more *(4)*, insertion of CH_2 into a second Si—Cl bond gives 1,1,2,2-tetrachloro-1,2-bis(chloromethyl)disilane *(6)* [b.p. 65—68 °C/0.3 torr, ^{1}H-NMR[6]: $\delta=3.35$ ppm (s), mass spectrum: $m/e=259$ ($Si_2C_2H_4{}^{35}Cl_5^+$)]; its constitution is proved by its reaction with methylmagnesium iodide to give 1,2-bis(chloromethyl)-1,1,2,2-tetramethyldisilane *(7)* [b.p. 65 °C/2 torr; ^{1}H-NMR: $\delta=0.2$ (12 H/s) and 2.9 ppm (4 H/s)], which had already been prepared by a different route[7].

$$(1) + CH_2N_2 \xrightarrow[-N_2]{Cu} \underset{(4)}{} (ClCH_2)Cl_2Si{-}SiCl_3 \xrightarrow[-N_2]{+(4)} (ClCH_2)Cl_2Si{-}SiCl_2(CH \quad (6)$$

$$(5)$$

$$Cl(CH_3)_2Si{-}Si(CH_3)_2Cl \xrightarrow{+(4)} ClCH_2(CH_3)_2Si{-}Si(CH_3)_2CH_2Cl$$

$$(8) \qquad (7)$$

Attempts to convert 1,2-dichloro-1,1,2,2-tetramethyldisilane *(8)* into *(7)* by reaction with *(4)* were unsuccessful. Analogous behavior was observed with the series of chloro(methyl)silanes, the reactivity towards *(4)* decreasing with increasing number of methyl groups and finally disappearing[3].

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Retention of the silicon-silicon bonds in all the carbene reactions described above was demonstrated, not only by analytical and spectral data of the isolated products, but also by spontaneous evolution of hydrogen on alkaline hydrolysis and reduction of Ag^{I} ions to metallic silver.

Pentachloro(trichloromethyl)disilane (2):

Phenyl(trichloromethyl)mercury (15 g, 38 mmol) was heated with hexachlorodisilane *(1)* (21 g, 77 mmol) and NaI (0.5 g) under argon for 6 h at 120 °C (bath temperature). The solid that separated was filtered off after addition of light petroleum. Fractional distillation of the filtrate gave pure *(2)*, b. p. 68 °C/0.6 torr (32% yield, 4.2 g), along with *(1)*, b. p. 25 °C/3 torr. The product *(2)* (4.0 g) was also obtained analogously from (bromodichloromethyl)-phenylmercury (15 g) and *(1)* (21 g).

IR (capillary; cm^{-1}): 860 s, 790 m, 732 vs, 702 s, 610 vs, 590 vs, 580 vs, 525 s, 498 s, 458 s, 448 m, 420 s, 360 s, and 342 m.

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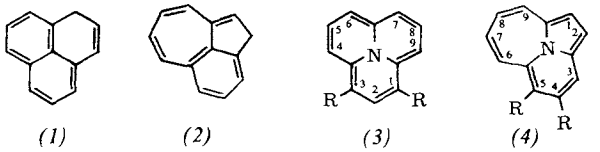
Diethyl Cycl[4.3.2]azine-4,5-dicarboxylate[**]

By *Wilhelm Flitsch* and *Bernhard Müter*[*]

The potential formation of a 12π electron periphery in the tricyclic arenes *(1)* and *(2)* and in the corresponding cyclazines *(3)* and *(4)*, respectively, confers a certain degree of similarity to antiaromatic systems on these compounds.

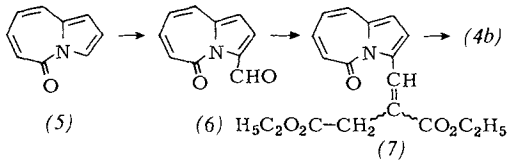
Both phenalene *(1)* and the isoelectronic compound 2*H*-benz[*cd*]azulene *(2)* possess a nonbonding molecular orbital[1,2b] so that, in spite of differing symmetries[3], the two compounds can form cations, anions, and radicals[2]. Symmetry-based differences between the two resonance systems appear mainly in the chemical properties of the compounds[2].



(1) *(2)* *(3)* *(4)*

(a), R = H; *(b)*, R = $CO_2C_2H_5$

Leaver et al.[4] described the cycl[3.3.3]azine *(3a)*, corresponding to the anion of *(1)*, and found it to be paratropic, in contrast to earlier expectations. A comparison of tricyclic arenes and hetarenes having a 12π periphery requires cycl-[4.3.2]azine *(4a)*, corresponding to the anion of *(2)*, the first derivative of which will now be described.



(5) *(6)* $H_5C_2O_2C-CH_2$ $CO_2C_2H_5$ *(7)* *(4b)*

The synthesis of the ester was accomplished starting from 3a-azaazulen-4-one *(5)* which we obtained by Wittig olefination of 2-pyrrolecarbaldehyde with 3-methoxycarbonyl-2-propenylidenetriphenylphosphorane and subsequent base-catalyzed cyclization[5]. A Vilsmeier reaction of *(5)* afforded *(6)* [yellow needles, m. p. 112 °C from benzene, 70% yield, IR: $\nu_{CO} = 1665, 1650\,cm^{-1}$] from which we obtained *(7)* [yellow oil, 50% yield, IR: $\nu_{CO} = 1735, 1710, 1670\,cm^{-1}$] by heating for 24 h with 1,2-bis(ethoxycarbonyl)ethylidenetriphenylphosphorane[7] in benzene. Two hours' heating in pyridine/piperidine (10:1) resulted in ring closure to give diethyl cycl[4.3.2]azine-4,5-dicarboxylate (diethyl 9b-azabenz[*cd*]azulene-4,5-dicarboxylate) *(4b)* [violet needles, m. p. 87 °C from light petroleum, 50% yield, IR: $\nu_{CO} = 1726, 1709\,cm^{-1}$][6].

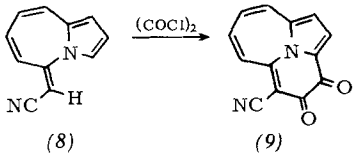
The ring proton signals appear at very high field in the NMR spectrum of *(4b)*, in spite of the two ester groups. The influence of the ester groups on the chemical shifts becomes apparent on comparison of the compounds *(3a)* and *(3b)* (Table 1).

Table 1. ^{1}H-NMR spectra (τ values) of compounds *(3a)* [4] in $[(CH_3)_3Si]_2O$, *(3b)* [4] in $CDCl_3$, and *(4b)* in CS_2.

Cpd.	1-H	2-H	3-H	4-H	5-H	6-H	7-H	8-H	9-H
(3a)	7.93	6.35	7.93	7.93	6.35	7.93	7.93	6.35	7.93
(3b)	—	2.84	—	3.23	3.86	4.77	4.77	3.86	3.23
(4b)	4.82	4.94	4.00	—	—	from 5.52 to			6.52

Like the isomeric cycl[3.3.3]azines, the cycl[4.3.2]azines are strongly paratropic. Symmetry-based differences between the two systems will only be clearly apparent when the NMR spectrum of *(4a)* becomes available. Nevertheless the nonuniform peripheral charge distribution expected for the nonalternant system *(4)* can already be seen from the properties of the two ester groups: two ν_{CO} bands are observed in the IR spectrum, and only one ester group undergoes transesterification on treatment with 5% methanolic sodium methoxide solution at the boiling temperature.

We were able to prepare a further cycl[4.3.2]azine derivative *(9)* in 10% yield by reaction of 4-cyanomethylen-3a-azaazulene *(8)*, obtainable from *(5)* and cyanomethylenetriphenylphosphorane[5], with oxalyl chloride in benzene (12 h, 25 °C). Compound *(9)* decomposes without melting



(8) *(9)*

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above 300 °C. NMR signals at $\tau = 1.7$—2.5 correspond to the ring protons. The position of the ν_{CO} bands (1645, 1610 cm^{-1}) accordingly indicates strong interaction between the CO groups and the π electrons of the ring system.

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[4] *D. Farquhar* and *D. Leaver*, Chem. Commun. 1969, 24.

[5] *W. Flitsch, B. Müter*, and *U. Wolf*, to be published.

[6] All compounds were characterized by their mass spectra and analytical data.

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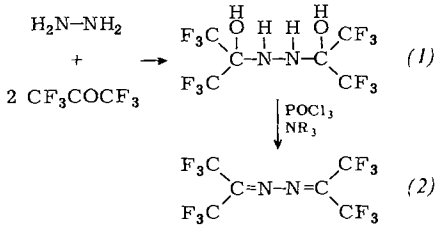
A Simple Synthesis of Hexafluoroacetone Azine[**]

By *Klaus Burger, Josef Fehn*, and *Willy Thenn*[*]

The syntheses previously reported for perfluorinated azines[1,2], in particular for hexafluoroacetone azine *(2)*[3-5], are complicated and proceed in several steps.

On direct treatment of hydrazine or hydrazine hydrate with an excess of hexafluoroacetone we obtained the diadduct *(1)*, which afforded hexafluoroacetone azine *(2)* by loss of water on treatment with phosphorus oxide trichloride and a tertiary amine (*e.g.* quinoline) at 0—15 °C. All the properties of the product agree with those previously recorded[3].



Hexafluoroacetone azine (2)

Hydrazine (3.2 g, 100 mmol) or its hydrate (5.0 g, 100 mmol) in methylene dichloride (100 ml) is treated with an excess of hexafluoroacetone with vigorous stirring in a closed apparatus and under a CO_2-cooled reflux condenser. The reaction is exothermic; cooling is necessary if the hexafluoroacetone is introduced very rapidly. Then the volatile products are removed at water-pump vacuum. The residue is added to ice-cooled quinoline (131 g, 1 mol) and thereafter treated with $POCl_3$ (38.1 g, 250 mmol) with vigorous stirring. The mixture is finally left at room temperature for 4—6 h and the product *(2)* is removed by condensation in a high vacuum. Purification is accomplished by fractional condensation or distillation through a short column. Yield 21.4 g (65%) of *(2)*.

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[3] *W. J. Middleton* and *C. G. Krespan*, J. Org. Chem. 30, 1398 (1965).

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Synthesis of 1,2λ^5-Azaphosphoridines[1][**]

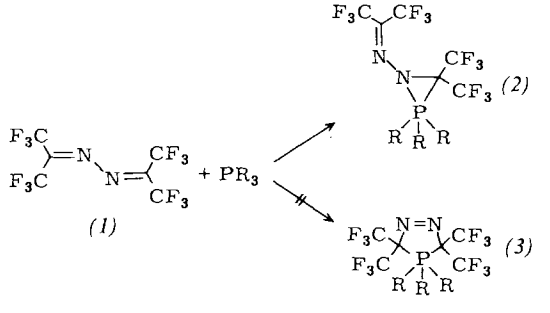
By *Klaus Burger, Josef Fehn*, and *Willy Thenn*[*]

Addition of criss-cross type is characteristic of azines[2] derived from aromatic aldehydes, cyclohexanone, cyclopentanone[3,4], or hexafluoroacetone[5], but examples of 1,2-[6] and 1,4-addition[7] are also known. A five-membered ring structure has been ascribed to an adduct of an azine and phosphorochloridic ester[8].

In anhydrous hexane at 0 °C hexafluoroacetone azine *(1)*[9] reacts with phosphorous esters or tris(dimethylamino)-phosphane to yield 1:1 adducts *(2)* (Table 1). These compounds have considerable thermal stability.

The ^{1}H-NMR spectra of *(2a)* and *(2b)* show signals for three equivalent *P*-alkoxy groups [(CCl_4, internal TMS) *(2a)*: $\delta = 3.75$ ppm (d), $J_{PH} = 11.7$ Hz]. The ^{19}F-NMR spectra [(CF_3COOH external) *(2a)*: $\delta = -0.32$ (m), -12.45 ppm (broad); *(2b)*: -0.78 (m), -12.65 ppm (broad)] also lie in the expected region[10]. These data contraindicate formation of the products by 1,4-addition *(3)* and suggest 1,2-addition to afford *(2)*.

The formation of the hitherto unrecorded 1,2λ^5-azaphosphoridine system[11] is further indicated by the ^{13}C-NMR spectra[12]. An unambiguous molecular peak, absence of the fragment $m/e = [M - N_2]^+$, and occurrence of the fragment $m/e = [M - (CF_3)_2CN]^+$ of intensity 100%, for *(2b)*, $m^* = 220.4$ (494→330), are further arguments in favor of structure *(2)*.



1-(Hexafluoroisopropylimino)-2,2,2-trimethoxy-3,3-bis(trifluoromethyl)-1,2λ^5-azaphosphoridine (2a)

Trimethyl phosphite (2.48 g, 20 mmol) is slowly added dropwise to a stirred solution of hexafluoroacetone azine *(1)*

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Table 1. Compounds *(2)* prepared. IR spectra determined as film on a Perkin-Elmer Infracord instrument.

Cpd.	R	B.p. [°C/torr]	Yield [%]	IR [cm^{-1}]
(2a)	OCH_3	83/12	96	1720 [a]
(2b)	OC_2H_5	96/12	90	1725 [a]
(2c)	$N(CH_3)_2$	$56/10^{-3}$	57	1720 [a]

[a] ν(C=N) in a $(CF_3)_2C{=}N-$ group [10].

(6.56 g, 20 mmol) in anhydrous hexane (40 ml) at 0 °C. After being kept for several hours at room temperature the mixture is fractionated; yield 8.7 g (96%) of *(2a)*.

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[1] Phosphorus Heterocycles with Pentacoordinated Phosphorus, Part 2.—Part 1: *K. Burger, J. Fehn,* and *E. Moll,* Chem. Ber. *104,* 1826 (1971).

[2] *D. Kolbah* and *D. Koruncev* in *Houben-Weyl-Müller:* Methoden der Organischen Chemie. Thieme, Stuttgart 1967, 4th Edit., Vol. 10/2, pp. 86ff.

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[4] *M. Häring* and *T. Wagner-Jauregg,* Helv. Chim. Acta *40,* 852 (1957); *T. Wagner-Jauregg* and *L. Zirngibl,* Chimia *22,* 436 (1968).

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[9] *K. Burger, J. Fehn,* and *W. Thenn,* Angew. Chem. *85,* 541 (1973); Angew. Chem. internat. Edit. *12,* 502 (1973).

[10] *W. J. Chambers, C. W. Tullock,* and *D. D. Coffman,* J. Amer. Chem. Soc. *84,* 2337 (1962); *W. J. Middleton* and *C. G. Krespan,* J. Org. Chem. *30,* 1398 (1965).

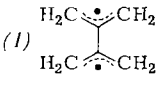
[11] *L. L. Muller* and *J. Hamer:* 1,2-Cycloaddition Reactions. Wiley, New York 1967, pp. 107ff.

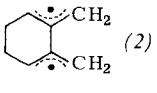
[12] *J. Firl* and *K. Burger,* unpublished work.

Diradicals as Intermediates in Chemical Reactions; 2,3-Dimethylene-1,4-cyclohexadiyl[1]

By *Wolfgang R. Roth* and *Gerhard Erker*[*]

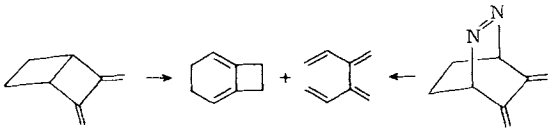
Tetramethyleneethane *(1)* has been repeatedly postulated as an intermediate in thermal rearrangements[3], and both a planar and an orthogonal arrangement have been discussed for its structure[4]. We have been interested in a derivative of *(1)*, namely 2,3-dimethylene-1,4-cyclohexadiyl *(2)*, in which the ethano bridge makes a planar or nearly planar geometry compulsory.

(1) 

 *(2)*

The anhydride of bicyclo[2.2.0]hex-5-ene-2,3-dicarboxylic acid[5] was converted into 2,3-dimethylenebicyclo[2.2.0]-hexane *(3)* by successive catalytic hydrogenation, reduction to the diol, conversion into the ditosylate, and elimination by potassium *tert*-butoxide/DMSO[6]. In the gas phase at 110 °C *(3)* rearranges to a mixture (67:33) of bicyclo[4.2.0]octa-1,5-diene *(4)*[7] and 3,4-dimethylene-1,5-hexadiene *(5)*[8].

A mixture of products of precisely the same composition was obtained on gas-phase thermolysis (110 °C) of 5,6-dimethylene-2,3-diazabicyclo[2.2.2]oct-2-ene *(6)*, which was obtained (m.p. 40 °C) in *ca.* 8% yield from dimethyl 1,2-dihydrophthalate through intermediacy of the diol, ditosylate, and *N*-phenyltriazolinedione adduct, the last-mentioned intermediate being subjected successively to catalytic hydrogenation, alkaline hydrolysis, elimination, and oxidation by $CuCl_2$.

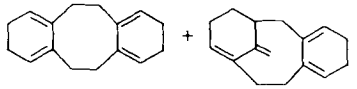


(3) *(4)* *(5)* *(6)*

An intermediate formation of *(3)* during decomposition of *(6)* can be excluded because, although *(3)* and *(6)* have comparable thermal stability, *(3)* is not formed on thermolysis of *(6)* in either a stationary or a flow system (detection by VPC).

The formation from either *(3)* or *(6)* of exactly the same product mixture, whose composition is independent of the reaction temperature and the pressure, indicates a common intermediate to which we ascribe the structure of the diradical 2,3-dimethylene-1,4-cyclohexadiyl *(2)*.

Unlike the gas-phase reaction, heating *(3)* or *(6)* at 110 °C in dilute cyclohexane solution affords mainly (*ca.* 65%) the dimers of *(2)*, accompanied by *ca.* 5% of the product

(3) →  ← *(6)*

(7) *(8)*

mixture *(4)* + *(5)* (67:33) and *ca.* 30% of polymer. The two main products of the dimer fraction, amounting together to about 80%, were isolated by gas chromatography; on the basis of their spectroscopic properties they are regarded as tricyclo[10.4.0.$0^{4,9}$]hexadeca-4,8,12,16-tetraene *(7)* and 15-methylenetricyclo[9.3.1.$0^{3,8}$]pentadeca-3,7,11-triene *(8)*[9].

The same dimers, free from the rearrangement products *(4)* and *(5)*, were formed on photolysis (Philips HPK 125, Pyrex filter) of *(6)* (0.1% solution in pentane), together with polymers.

On irradiation of a 1 M solution of *(6)* in hexafluorobenzene at −180 °C in an EPR spectrometer a progressively broadening singlet is overlaid by a triplet spectrum that can be ascribed to *(2)*: A six-line spectrum (D=0.0204 cm^{-1}; E=0.00159 cm^{-1}) appears centered at 3300 gauss and the (Δm=2) transition with lower intensity at 1650 gauss[10].

This triplet species observed in the EPR spectrum seems to be responsible for dimer formation. Thus, if either *(3)* or *(6)*, dissolved in hexachlorobutadiene, is thermolyzed in the preheated probe of an NMR instrument, intense emission signals corresponding to the absorption signals of the dimers are observed. The same nuclear polarized spectra are recorded on photolysis of *(6)*, in solution in hexachlorobutadiene, if this is carried out in the NMR apparatus[11].

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A necessary condition for the occurrence of the CIDNP signals is that at least one reactant in the dimer formation shall be in a triplet state[12]. In view of the EPR experiments the intermediate *(2)* can fill this role. The second reactant can be either a similar triplet molecule or a molecule of starting material. Indications that the dimerization occurs preferentially between two triplet molecules are provided by the facts that the CIDNP signals appear only in emission[11] and further that on thermolysis or photolysis of *(3)* or *(6)*, respectively, the triplet diradical cannot be trapped by 1,3-cyclohexadiene or 1,2-dimethylenecyclohexane.

That *(2)* reacts differently according to whether it is produced in the gas phase or in solution may be an expression of a difference in spin multiplicities. In the gas phase the conversion into the triplet state occurs only slowly and cannot compete with the rate of formation of *(4)* and *(5)*; but in solution the intersystem crossing probability is very much greater and we observe the reactions of the triplet.

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[1] We thank Prof. *W. Grimme* for informing us of his independent work on this problem [2].

[2] *W. Grimme* and *H. J. Rother*, Angew. Chem. *85*, 512 (1973); Angew. Chem. internat. Edit. *12*, 505 (1973).

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[7] The spectroscopic properties of all the new compounds are in accord with the structures here assigned.

[8] *L. Skattebøl* and *S. Solomon*, J. Amer. Chem. Soc. *87*, 4506 (1965).

[9] The spectroscopic properties of *(7)* and *(8)* differ from those reported by *Bauld* and *Chang* [6] for the Diels-Alder adducts of *(3)*.

[10] We thank Prof. *D. Schulte-Frohlinde*, Mülheim/Ruhr, for recording this spectrum.

[11] We thank Prof. *L. J. Oosterhof* and Dr. *R. Kaptain*, Leiden, for carrying out this experiment and for help in interpreting its result.

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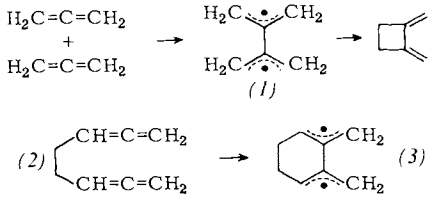
Mechanism of Allenic Dimerization

By *Wolfgang R. Roth*, *Margerita Heiber*, and *Gerhard Erker*[*]

Tetramethyleneethane *(1)* has been repeatedly postulated as an intermediate in allenic dimerization[1]. We have sought proof of this hypothesis in the case of 1,2,6,7-octatetraene *(2)*, which if it reacts analogously should give rise to the diradical 2,3-dimethylene-1,4-cyclohexadiyl *(3)*. The behavior of *(3)* in the gas phase and in solution has already been described[2].



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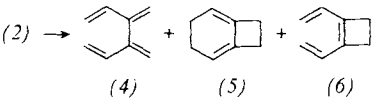
According to *Skattebøl* and *Solomon*[3], *(2)* rearranges at 310 °C to 2,3-dimethylene-1,5-hexadiene *(4)*. We have now observed that thermolysis of *(2)* in the gas phase at 120 °C leads, not only to *(4)*, but also to bicyclo[4.2.0]octa-1,5-diene *(5)* and 1,2-divinyl-1-cyclobutene *(6)*[4]. The rearrangement is strictly first order and is characterized by the activation parameters $E_a = 24.8 \pm 0.2$ kcal mol^{-1} and $A = 0.9 \times 10^{10}\,s^{-1}$.



The relative concentrations of the rearrangement products are independent of the reaction temperature (80—150 °C) but not of the pressure. Whereas *(4)* is formed almost exclusively below 10^{-2} torr, yet at *ca.* 1 torr product ratios of *ca.* 60:25:15 are observed for the isomers *(4)*, *(5)*, and *(6)* and are shifted in favor of *(5)* by increasing pressures, so that in solution (infinitely high pressure) the ratios 40:60:0 are attained.

This pressure-dependence can be understood if the rearrangement of *(2)* is formulated as proceeding *via* a vibrationally excited intermediate to which we assign the structure *(3)*[5]. If the intermediate is able to get rid of its excess energy sufficiently rapidly by collision (high pressure), then we find that the ratio for *(4)*:*(5)* is very close to that expected from *(3)* which is 33:67[2]. As the pressure is lowered, *(3)* transfers increasing amounts of its excess energy to its rearrangement products *(4)* and *(5)*, which, insofar as they are not deactivated by collision, can either regenerate *(3)* or afford divinylcyclobutene *(6)*.

As shown in independent experiments, *(6)* rearranges at 170 °C to a mixture of *(4)* and *(5)*, and at 250 °C *(5)* passes irreversibly into *(4)*. The formation of *(6)* from *(4)* and/or *(5)* thus appears to contradict thermodynamics, but it becomes intelligible if one remembers that equilibrium conditions do not exist in this middle pressure range. At very low pressures, which provide a sufficient lifetime for the excited molecule to equilibrate, we observe the expected, almost exclusive formation of the thermodynamically most stable product *(4)*.

Thermolysis of *(2)* in solution (cyclohexane, 120 °C) affords, along with *(4)* and *(5)*, a *ca.* 30% yield of the dimerization products of the triplet diradical *(3)*[2]. If this reaction is carried out in the NMR spectrometer, CIDNP signals of the dimers appearing in emission can be recorded. That the ratio of triplet to singlet reaction[2] is distinctly less than for 2,3-dimethylenebicyclo[2.2.0]hexane or 5,6-dimethylene-2,3-diazabicyclo[2.2.2]oct-2-ene can be due to the vibrationally excited state of *(3)*, through which the lifetime of the diradical is shortened and the chance of transition to the triplet is lessened.

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[1] *J. E. Baldwin* and *R. H. Fleming*, Fortschr. Chem. Forsch. *15*, 281 (1970).

[2] *W. R. Roth* and *G. Erker*, Angew. Chem. *85*, 510 (1973); Angew. Chem. internat. Edit. *12*, 503 (1973).

[3] *L. Skattebøl* and *S. Solomon*, J. Amer. Chem. Soc. *87*, 4506 (1965).

[4] The spectroscopic properties of all new compounds are in accord with the assigned structure.

[5] The postulated excess energy of *(3)* can be estimated at *ca.* 25 kcal mol^{-1} by consideration of the changes in bond energy (replacement of two π- by one σ-bond: 50 kcal mol^{-1}), the gain in resonance

energy (2×12 kcal mol^{-1}), the removal of allene strain (2×13 kcal mol^{-1} [6]), and the observed activation energy.

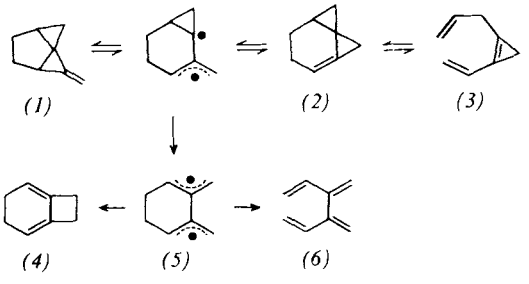
[6] *G. B. Kistiakowsky, J. R. Ruhoff, H. A. Smith*, and *W. E. Vaughan*, J. Amer. Chem. Soc. *58*, 146 (1936).

Thermal Rearrangement of 2-Methylenetricyclo[4.1.0.0^{1,3}]heptane

By *Wolfgang R. Roth* and *Gerhard Erker*[*]

Seeking methods for preparation of the diradical 2,3-dimethylene-1,4-cyclohexadiyl *(5)*[1] we became interested in the thermolysis of 2-methylenetricyclo[4.1.0.0^{1,3}]heptane *(1)*[2].

If *(1)* is heated in the gas phase (1 torr) at 120 °C, the compound is converted by a methylenecyclopropane rearrangement[3] into an isomeric compound which we regard as tricyclo[5.1.0.0^{1,3}]oct-3-ene on the basis of its spectroscopic properties. At 150 °C a third member of the equilibrium mixture appears, and this was identified as 1-allyl-2-vinyl-1-cyclopropene *(3)* which is connected with *(2)* by an intramolecular Diels-Alder reaction.



(1) *(2)* *(3)* *(4)* *(5)* *(6)*

At 180 °C the equilibrium mixture of *(1)*, *(2)*, and *(3)* rearranges irreversibly into a mixture of bicyclo[4.2.0]octa-1,5-diene *(4)* and 3,4-dimethylene-1,5-hexadiene *(6)*. Although the ratio of *(4)* and *(6)* produced is independent of reaction temperature and it is thus unlikely that *(4)* and *(6)* are formed by competing parallel reactions, yet a pronounced dependence on pressure is observed: below 10^{-2} torr the tetraene *(6)* is formed almost exclusively; as the pressure is increased the concentration of *(6)* decreases continuously in favor of *(4)*, until at 100 torr the ratio is *ca.* 1:1.

The formation of *(4)* and *(6)* can be understood if it proceeds through the intermediacy of the diradical 2,3-dimethylene-1,4-cyclohexadiyl *(5)* which, in view of the pressure-dependence of the product ratio, must apparently be formed in a vibrationally excited state. Owing to this excess energy the rearrangement products *(4)* and *(6)* can be converted one into the other, insofar as they are not deactivated by collision, so that reaction leads to preferential formation of the thermodynamically most stable product *(6)*. In the middle pressure range also 1,2-divinyl-1-cyclobutene should be formed by secondary rearrangement of the excited products; this compound is, however, unstable at 180 °C and can then no longer be detected owing to its rearrangement to *(4)* and *(6)*[4].

Further support for the intermediate occurrence of the diradical *(5)* is found in the thermolysis of *(1)* in cyclohexane: besides polymers one obtains the dimerization products of the triplet diradical; and if this reaction is carried out in the NMR spectrometer CIDNP signals of the dimers appearing in emission can be observed here also[1].

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The Diradical 2,3-Dimethylene-1,4-cyclohexadiyl as Intermediate in Thermal Gas Phase Rearrangements[**]

By *Wolfram Grimme* and *Heinz-Joachim Rother*[*]

The mechanism of the dimerization of allene to 1,2-dimethylenecyclobutane appears dualistic. The stereospecificity of the reaction demonstrated for one case[1] is best accounted for by a concerted process controlled by the orbital phases[2], whereas an isotope effect[3] applying to the product distribution but not to the reaction rate indicates the intermediacy of the 2,3-dimethylenetetramethylene diradical. In the latter case stereospecificity would result only if formation and cyclization of the diradical obeyed the selection rules[2]. This condition appears to be fulfilled for the second reaction step since, in the degenerate dimethylenecyclobutane rearrangement, the 2,3-dimethylenetetramethylene diradical (also described as "tetramethyleneethane") is formed and cyclizes again conrotatorily[4]. We have studied allenic dimerization for an intramolecular case since there the 2,3-dimethylenetetramethylene diradical formed as intermediate is limited as to its geometry and the rotatory sense of cyclization.

Skattebøl and *Solomon*[5] have described the thermal rearrangement of 1,2,6,7-octatetraene *(5)* to 3,4-dimethylene-1,5-hexadiene *(8)*. They do not record any direct "dimerization product" containing the dimethylenecyclobutane partial structure but discuss the diradical 2,3-dimethylene-1,4-cyclohexadiyl *(6)* as intermediate.

We repeated the thermolysis of *(5)* in the inlet port of a gas chromatograph and found that, between 250 and 300 °C with 5 to 50% conversion, the product *(8)* is accompanied by bicyclo[4.2.0]octa-1,5-diene *(9)* [NMR (CCl_4, TMS internal): $\tau = 4.84$ (2H), 7.30 (4H), 7.88 ppm (4H); UV (in cyclohexane): $\lambda = 271$ nm ($\varepsilon = 5100$); dehydrogenated to benzocyclobutene by tetrachloro-*o*-benzoquinone]. The kinetically controlled product ratio *(8)*:*(9)* between 250 and 300 °C amounts to $(1.05 \pm 0.05):1$; it increases at higher temperatures since above 330 °C *(9)* passes into *(8)*. The diradical 2,3-dimethylene-1,4-cyclohexadiyl *(6)* can reasonably be regarded as the precursor of both products if the two extreme conformations are taken into consideration: The chair conformation with two twisted allyl groups *(6a)*, which is the primary product of union of the allene units, possesses in the two 2p-orbitals

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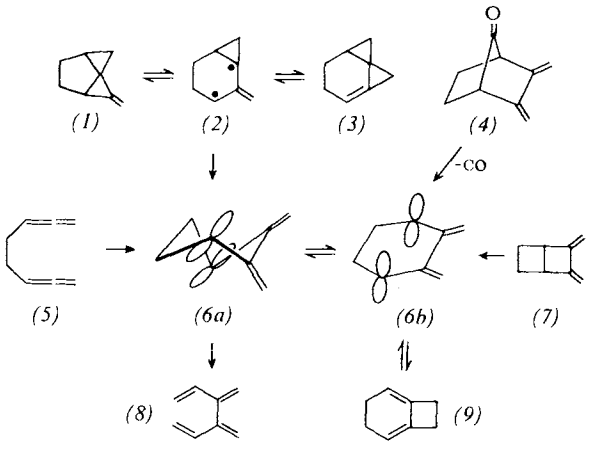
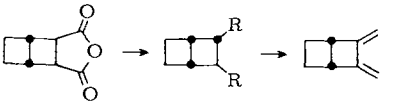
of the ring that are both parallel to the 5,6-bond the prerequisite for ring opening to form *(8)*. In the planar 2,2'-bisallyl diradical *(6b)*, however, the way to conversion into *(9)* is open and should, according to theory, occur by disrotation.



To confirm the occurrence of *(6)* in thermolysis of the "bisallene" *(5)*, we attempted to produce *(6)* by a different route. We found that, on stationary thermolysis in the gas phase above 105 °C, 2-methylenetricyclo[4.1.0.0^{1,3}]-heptane *(1)*[7] is in equilibrium with tricyclo[5.1.0.0^{1,3}]oct-3-ene *(3)* [NMR (CCl_4, TMS internal): $\tau = 4.35$ (1H), 7.49 (1H, A part of an AB system), 7.7—8.3 (4H), 8.46, 8.73 (2H, AB system), 8.5—8.9 (1H), 9.10 ppm (1H, t)]. The rate constants for the initial stages of the forward and reverse reaction at 105 °C afford the equilibrium constant $K = [(1)]:[(3)] = 0.9 \pm 0.2$. The equilibration is a methylenecyclopropane rearrangement[8] whose intermediate *(2)*, being of methylenetrimethylene diradical type, would be expected to be readily convertible into the diradical *(6)* by opening of the three-membered ring. Experimentally both *(1)* and *(3)*, under the above-mentioned conditions for flow-thermolysis, gave, in addition to their equilibrium partner and a product of subsequent reaction of *(3)* (which we regard as 1-allyl-2-vinyl-1-cyclopropene), the compounds *(8)* and *(9)* in the ratio 1.05:1 as obtained previously. These results indicate that *(6)* is formed as intermediate in both reactions. It is further necessary to require that the diradical is formed in the chair conformation *(6a)* also from the equilibrium mixture of methylenespiropentanes *(1)* and *(3)*; this geometry is achieved if both cyclopropane rings of *(1)* open with one orbital remaining orthogonal to the π-system, as is the case in the methylenecyclopropane rearrangement[8].

A further precursor of the diradical *(6)* could be 2,3-dimethylenebicyclo[2.2.0]hexane *(7)*, from which the planar conformation *(6b)* could arise on disrotatory opening[6] of the central bond. We prepared this compound by analogy with the synthesis of 5,6-dimethylenebicyclo[2.2.0]hex-2-ene[9], starting from the anhydride *(10)*[10] of bicyclo[2.2.0]hexane-*exo*-2,3-dicarboxylic acid. After esterification of *(10)* with HCl in methanol, isomerization by sodium methoxide in the same solvent afforded the dimethyl *trans*-dicarboxylate *(11)*[11] (m.p. 49 °C, 90%). Reduction with $LiAlH_4$ then gave the diol *(12)* as a viscous oil (b.p. 88—90 °C/10^{-4} torr, 94%), which provided the ditosylate *(13)* (m.p. 79 °C, 80%) on esterification by *p*-toluenesulfonyl chloride in pyridine. When *(13)* was treated with potassium *tert*-buto ide in dimethyl sulfoxide and the mixture was distilled at room temperature and 0.1 torr, 2,3-dimethylenebicyclo[2.2.0]hexane *(7)*[12] collected in 78% yield in a trap cooled to −78 °C [NMR (CCl_4, TMS internal): $\tau = 4.85$ (2H, s), 5.30 (2H, s), 6.7 (2H, m), 7.2—8.2 ppm (4H, m); UV (in cyclohexane): $\lambda = 243$ ($\varepsilon = 9500$, sh), 252 (11000), 260 nm (8000, sh)].



In the inlet port of the gas chromatograph at 150 °C *(7)* rearranges to *(8)* and *(9)*. The mass balance of 80% shows that rearrangement of the compound in the gas phase is largely intramolecular, whereas dimers are formed on thermolysis in solution[13]. Between 170 and 300 °C the product ratio *(8)*:*(9)* amounts to (0.45 ± 0.02):1, *i.e.* twice as much *(9)* is formed as when starting from *(5)*. This difference accords with our assumption that *(7)* forms primarily the planar diradical *(6b)*, from which *(9)* then arises.

The diradical 2,3-dimethylene-1,4-cyclohexadiyl is thus proved to be a very reactive intermediate, which in the gas phase reacts further before reaching its conformational equilibrium, yielding the dimethylenehexadiene *(8)* from the chair conformation with twisted allyl units, and the bicyclo[4.2.0]octadiene *(9)* from the planar conformation.

Finally it should be mentioned that no conclusion can be drawn about the conformation of the diradical *(6)* when this is formed by thermal fragmentation of 2,3-dimethylene-7-norbornanone *(4)*[14] since at the required temperature (≥ 430 °C in the inlet port of the gas chromatograph) the product *(9)* is largely converted into its isomer *(8)*.

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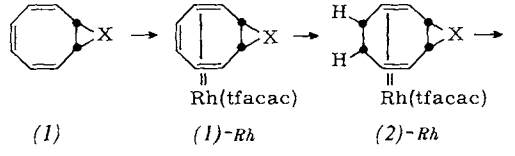
Cope Rearrangement of *cis*-Bicyclo[6.1.0]-nona-2,6-diene and Its 9-Hetero Analogs[**]

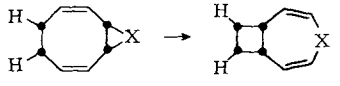
By *Wolfram Grimme* and *Klaus Seel*[*]

cis-Divinyl-substituted three-membered rings undergo the Cope rearrangement very readily, but the rate of their reaction varies characteristically with the nature of the ring atoms. For example, all attempts to synthesize *cis*-divinylcyclopropane[1] at reaction temperatures down to −40 °C gave only its rearrangement product 1,4-cycloheptadiene, and analogously an attempt to isolate 1-ethyl-*cis*-divinylaziridine[2] at 50 °C was unsuccessful. *cis*-Divinyloxirane[3], however, is known and undergoes Cope rearrangement to 4,5-dihydrooxepin only above 75 °C. A similar stabilizing effect is shown by benzene oxide[4], which opens to the seven-membered ring with a higher activation energy than is needed for dimethyl 7,7-norcaradienedicarboxylate[5]. To date there have been no quantitative results published for the differential reactivity of a series of heteroanalogous *cis*-divinyl-substituted three-membered ring compounds.

We have recently prepared *cis*-bicyclo[6.1.0]nona-2,6-diene *(2a)* by selective catalytic hydrogenation of *cis*-bicyclo[6.1.0]nona-2,4,6-triene *(1a)* protected by the 1,1,1-trifluoro-2,4-pentanedionatorhodium(I) group[6]. In spite

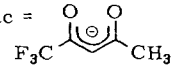


(1) *(1)-Rh* *(2)-Rh*



(2) *(3)*

(a), X = CH_2
(b), X = O
(c), X = $N\text{-}CO_2C_2H_5$
-D, H = D

tfacac = 

of its *cis*-divinylcyclopropane structural unit this compound is stable at 0 °C and transforms only slowly at room temperature into *cis*-bicyclo[5.2.0]nona-2,5-diene *(3a)*[7]. This deceleration of the Cope rearrangement is caused by steric compression as well as by a lower reaction energy; it was shown by stereoselective deuteration that the transition state connects the coiled conformations of *(2a)* and *(3a)* with one another[6].

This process of selective hydrogenation, when applied to 9-oxabicyclo[6.1.0]nona-2,4,6-triene *(1b)*[8] and ethyl 9-azabicyclo[6.1.0]nona-2,4,6-triene-9-carboxylate *(1c)*[9], yielded 9-oxabicyclo[6.1.0]nona-2,6-diene *(2b)* and ethyl 9-azabicyclo[6.1.0]nona-2,6-diene-9-carboxylate *(2c)*, respectively. The melting points of the olefins protected by the organorhodium group, and the yields on introduction and removal of this group, are collected in Table 1.

The compound *(2b)*, which is stable at room temperature, rearranges at 90 °C to 4-oxabicyclo[5.2.0]nona-2,5-diene *(3b)*. However, *(2c)* is stable only up to −10 °C and

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Table 1. Selective reduction of 9-heterobicyclo[6.1.0]nonatrienes *(1b)* and *(1c)*.

Starting cpd.	*(1)-Rh* Yield [%]	M. p. [°C]	*(2)-Rh* Yield [%]	M. p. [°C]	*(2)* Yield [%]
(1b)	85	160	80	174	92
(1c)	41	133	88	111	76

passes into ethyl 4-azabicyclo[5.2.0]nona-2,5-diene-4-carboxylate *(3c)* already at 0 °C. The structures of the new heterocycles follow from comparison of the NMR spectra (Table 2) with those of the alicyclic analogs *(2a)* and *(3a)*[6].

Table 2. NMR signals of the heterobicyclononadienes, measured in CCl_4 at 60 MHz with TMS as internal standard. Chemical shifts are in ppm (τ), coupling constants in Hz.

Cpd.	Vinyl-H	Methine-H	Methylene-H	
	AB system (*J*)	Singlet	Multiplet	
(2b)	4.30, 4.62 (12)	6.60	7.3—8.1	
(2c)	4.29, 4.58 (10)	6.92	7.1—8.3	
	AX system (*J*)	Multiplet	Multiplet	Multiplet
(3b)	3.85, 5.39 (8.5)	6.9	7.6—8.1;	8.1—8.7
(3c)	3.20, 5.16 (10)	6.9	7.6—8.2;	8.2—8.7

The Cope rearrangement of all three bicyclo[6.1.0]nonadienes *(2)* occurs in one direction only, giving the bicyclo[5.2.0]nonadiene systems *(3)*. It is stereospecific between the coiled conformations of the starting and terminal compounds: as for the carbocycle[6], so also for the labeled compounds *(2b)-D* and *(2c)-D* the deuterium atoms that are *syn* on the eight-membered ring remain *syn* on the four-membered ring of the rearrangement products.

We have applied kinetic analysis to the Cope rearrangements of *(2a)—(2c)*, these being comparable in mechanism and geometry. For this purpose samples of each compound, dissolved in CCl_4, were rearranged in a thermostat at four temperatures and the compositions were investigated ten times in each run by NMR spectroscopy at −20 °C. Applying the method of least squares to the experimental data gave three sets of first-order rate constants with a correlation of ≥0.98; the constants of the Arrhenius equations are given in Table 3.

Table 3. Arrhenius constants for the Cope rearrangement of bicyclo[6.1.0]nona-2,6-dienes. Limits of error are standard deviations.

Cpd.	*T* [°C]	log *A*	E_a [kcal mol^{-1}]
(2a)	35—48	13.25	25.0±0.50
(2b)	91—105	12.89	28.6±0.85
(2c)	0—17	12.35	21.3±0.60

The results show that the decreases in the rates of the Cope rearrangements *(2c)>(2a)>(2b)* are due mainly to a difference of *ca.* 3.6 kcal mol^{-1} in each pair of activation energies. The sequence in this series does not correspond to the enthalpies of reaction since $\Delta\Delta H_f^0$ is found to be lowest for the carbocycle by summation of bond increments[10]; this result is supported by the reversible rearrangement of the 9-methylbicyclo[6.1.0]nonadienes[6]. There is as yet no satisfactory explanation for the differential (here displayed quantitatively for one example) beha-

vior of the C—C bonds in cyclopropane and its hetero analogs in pericyclic reactions.

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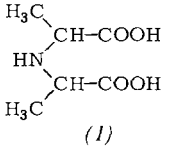
Determination of the Structure of the Vanadium Compound, Amavadine, from Fly Agaric

By *Helmut Kneifel* and *Ernst Bayer*[*]

We have isolated from fly agaric, *Amanita muscaria,* a pale blue compound containing vanadium[1] which we call amavadine. Elemental analysis gave the composition $C_{12}H_{20}N_2VO_{11}\cdot H_2O$. The molecular weight was determined as 415[1]. According to the ESR and IR spectra the vanadium is quadrivalent in the form of a $>VO$ group[1]. It has not proved possible to remove and isolate the chelating organic ligands of amavadine. Determination of the structure is made still harder by the low volatility of the compound which prevented us obtaining a mass spectrum and by the paramagnetism which precluded the use of NMR spectra.

Hydrolysis of amavadine by 6 N hydrochloric acid affords mainly L-alanine. In 1 N sodium hydroxide solution sodium pyruvate and acetaldehyde are formed as well as alanine. Reduction of amavadine by zinc and acetic acid yielded α,α'-iminodipropionic acid *(1)*. The identities



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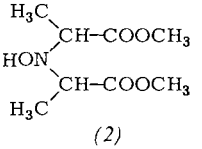
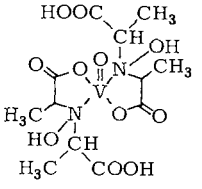


(2)

of all the degradation products were proved by mass spectrometry, nuclear resonance, preparation of derivatives and comparison of these with authentic specimens. Assuming an iminodipropionic acid derivative to form a 2:1 complex with the vanadyl group shown to be present, and the sixth coordination position to be occupied by water, it remains only to assign one additional oxygen atom per iminodipropionic acid residue. Iminodipropionic acid itself is not the complexing agent, as was shown by comparison of amavadine with the vanadyl complex of *(1)* which we synthesized.

The first indication about the additional oxygen atoms came from ESR spectroscopic detection of a nitroxyl radical on oxidation of amavadine in an alkaline medium. Finally a dimethyl ester $C_8H_{15}NO_5$ was isolated after methanolysis of amavadine in methanol/H_2SO_4; this was identified as dimethyl *N*-hydroxy-α,α'-iminodipropionate *(2)* by means of its mass spectra and degradation reactions.

N-Hydroxy-α,α'-iminodipropionic acid was prepared by treating hydroxyammonium chloride with α-bromopropionic acid at pH = 10 and purification by ion-exchange chromatography on a weakly basic resin AG 3 X 4 (Biorad). Reaction of this compound with vanadyl sulfate in water gave a complex *(3)* that was identical with amavadine in chromatographic behavior, electron spin resonance, electronic spectrum, and positions of the IR absorptions. The synthetic complex differs only in its chirality from the natural complex whose two optically active carbon atoms exist in the L-configuration (see above).



(3)

It cannot be excluded that in the fungal mycellium of *Amanita muscaria* the amavadine may be fixed as a metal proteide to a macromolecular component, this loose fixation being destroyed during the isolation[2].

Amavadine is the first naturally occurring vanadium compound whose structure has been elucidated. It shows no apparent similarity to the, admittedly not yet fully clarified, blood pigment of the tunicates, hemovanadin[3].

The structure of the complexing agent is remarkable as being a new ligand in both natural and synthetic chelates.

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Transmetalation and Double Metal Exchange: A Convenient Route to Organolithium Compounds of the Benzyl and Allyl Type[**]

By *Manfred Schlosser* and *Jürgen Hartmann*[*]

In the presence of potassium *tert*-butoxide, *n*-butyllithium metalates even such weakly acidic hydrocarbons as benzene[1], arylalkanes[1,2], and alkenes[1–3]. In those cases where this metal/hydrogen exchange leads to a resonance-stabilized organometallic species, it is an organo*potassium* compound that precipitates[2,4]. The initially accompanying lithium *tert*-butoxide can be completely removed by wash-

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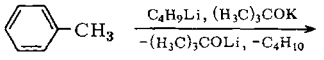
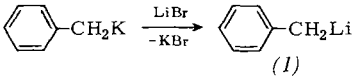
ing with benzene or toluene, in which it is sufficiently soluble.

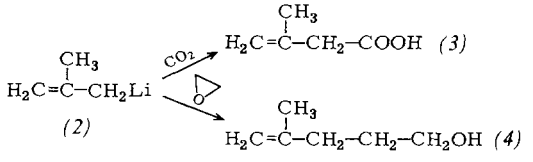
On treatment with an equivalent amount of lithium bromide[5] the pure organopotassium residue is converted into a soluble organolithium compound and insoluble potassium bromide[6]. Thus it is possible to prepare benzyllithium *(1)* (89%) from toluene and to eliminate all by-products by filtration. This material can be stored longer than when prepared conventionally[7].





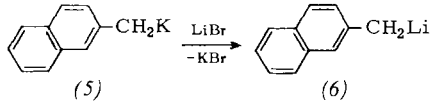
(1)

Starting from isobutene the procedure afforded pure 2-methylallyllithium *(2)* which was converted into the acid *(3)* (60%) and the alkenol *(4)* (72%).



(2)

However, organometallic compounds with a bulky organic moiety, such as 2-naphthylmethylpotassium *(5)*, are themselves too soluble to permit selective removal of the alkoxide by washing. In such cases one has to employ the organopotassium compound or, after metal exchange, the organolithium compound *(6)* in the presence of lithium *tert*-butoxide[8].



(5) *(6)*

Activation with potassium *tert*-butoxide has a definite advantage over the principally equivalent activation with tetramethylethylenediamine (TMEDA)[9,10]. Numerous reactions, such as addition to enolizable ketones and nitriles as well as stereoselective diene polymerizations[11], are only possible in the absence of highly electropositive metals and powerful solvating agents. Once present, TMEDA remains strongly associated with the organolithium compound[9,12]. In contrast, the metal introduced by potassium *tert*-butoxide can be completely removed by subsequent exchange with lithium, the activation thus being "switched off" again.

Benzyllithium (1)

Twice sublimed potassium *tert*-butoxide (100 mmol) was suspended in dry toluene (100 ml) under an inert gas in a three-necked flask fitted with a sintered glass exit[13]. Dropwise addition of an equivalent of *n*-butyllithium (15% solution in hexane) produced a bright red precipitate. After 30 minutes' stirring the solution was pressed through the glass frit, the residue treated with fresh toluene (100 ml), and the solution again allowed to pass through the glass frit. The washing process was repeated twice. The residual red solid was dried for 1 hour at 0.3 torr; diethyl ether (200 ml) was then added at −78 °C and while the mixture was warmed to room temperature dry LiBr (100 mmol) was also added. The insoluble KBr was removed by filtering the orange-yellow solution through the frit into a Schlenk burette. Back titration[14] with 1,2-dibromoethane indicated a yield of 85%; derivatization with trimethylchlorosilane afforded 89% of benzyltrimethylsilane[15] (gas-chromatographic comparison with authentic material[16]: 2.5 m 20% Apiezon L, 100—230 °C; decane as "internal" standard, weight-based calibration factor: 2.1). According to flame spectrometry the Li/K ratio was 44 : 1; the proportion of potassium can be further reduced by retreatment with LiBr.

Isobutenyllithium (2)

Modifying the procedure given above, the metalation was carried out at −20 °C. The excess of isobutene was allowed to evaporate, and the residue was washed with benzene instead of toluene. Since it is practically insoluble in diethyl ether, the yellow isobutenylpotassium was taken up in tetrahydrofuran and treated with LiBr. Double titration indicated a yield of 80%; no potassium could be detected in the hydrolyzed product, either by flame spectrometry or by Kalignost precipitation. Carboxylation yields 3-methyl-3-butenoic acid *(3)*[15] (60%; b.p. 67—68 °C/17 torr) and treatment with ethylene oxide at 0 °C gives 4-methyl-4-penten-1-ol *(4)*[15] (72%; b.p. 144—146 °C/760 torr).

2-Naphthylmethylpotassium (5)

2-Methylnaphthalene was metalated as described for benzyl lithium, except that only a stoichiometric amount of the hydrocarbon was employed. Carboxylation converts the resulting blackish red solution into 2-naphthylacetic acid[15] (75%; m.p. 139—141 °C; ref. [17]: 137—139 °C).

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[3] However, we did not succeed in metalating saturated hydrocarbons such as octane and cyclohexane, either with butyllithium in the presence of potassium *tert*-butoxide or with butylpotassium, obtained from dibutylmercury. A report to the contrary by *R. A. Finnegan* (Tetrahedron Lett. *1963*, 429) should therefore be viewed with skepticism.

[4] *L. Lochmann*, personal communication (1967).

[5] Lithium perchlorate is unsuitable because it partially oxidizes organometallic compounds to alkoxides.

[6] Conversions of organometallic compounds with metal salts: *R. G. Jones* and *H. Gilman*, Chem. Rev. *54*, 847 (1954).

[7] The method of preparation most commonly used hitherto (*D. Seyferth, R. Suzuki, C. J. Murphy*, and *C. R. Sabet*, J. Organomet. Chem. *2*, 431 (1964)) yields benzyllithium in the presence of tetramethylstannane, with which we have found it to undergo slow decomposition to ethylbenzene.

[8] *(6)* is also accessible by treatment of 2-methylnaphthalene with *n*-butyllithium in tetrahydrofuran (5 h at 0 °C, 75% yield) and with *sec*-butyllithium in diethyl ether (48 h at −35 °C, 50%) or tetrahydrofuran (9 h at −78 °C; 65%). Side products, arising *inter alia* from ether decomposition and addition of *sec*-butyllithium to the liberated ethylene, are unavoidable.

[9] *G. G. Eberhardt* and *W. A. Butte*, J. Org. Chem. *29*, 2928 (1964).

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[12] Cf. also *J. J. Brooks* and *G. D. Stucky*, J. Amer. Chem. Soc. *94*, 7333 (1972); *R. P. Zerger* and *G. D. Stucky*, Chem. Commun. *1973*, 44.

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[14] *H. Gilman* and *F. Schulze*, J. Amer. Chem. Soc. *47*, 2002 (1925).

[15] Mass spectra, NMR data, and microanalyses confirm the assumed structures.

[16] *C. R. Hauser* and *C. R. Hance*, J. Amer. Chem. Soc. *73*, 5846 (1951).

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The Primary Processes of Photosynthesis

By *Gernot Renger*[*]

The overall process of photosynthesis is divided, spatially and functionally, into two large sections:

A) The system of the primary processes of photosynthesis characterized by a high structural organization within membranes. In this system, induced by light-activated photogenerators, $NADP^+$ is reduced with water as donor, leading to the evolution of O_2. The process is coupled with an ATP synthesis.

B) The Calvin cycle, which leads *via* enzyme reactions in a liquid plasma phase to the reduction of CO_2 with NADPH and ATP. Light is not required for these reactions.

Introduction of flash-photometric and flash-polarographic methods made it possible to analyze the elementary reactions taking place within the system of the primary processes[1]. These investigations led to the following picture of the functions of the above mentioned system[2]:

1. There exists an adaptation system (consisting of *ca.* 500 chlorophyll molecules together with additional accessory pigment molecules in each electron-transport chain) which allows the optimal adaptation to the flow of light quanta *via* energy-transfer mechanisms. At low light intensities the quanta are trapped over a large cross sectional area and are transferred to the reactive centers; and at high light intensities the excess quanta are exhausted out of the system, thereby avoiding an irreversible photodestruction[3].

2. Electron transport is driven by two photogenerators operating in series. In the photogenerators I (excitable by $\lambda < 730$ nm) and II (excitable by $\lambda < 700$ nm) an excited electronic state leads to a geometrically defined charge separation forming electrons and holes. The primary electrons and holes induce secondary electron-transfer reactions. The holes produced by photogenerator II oxidize H_2O to O_2 by a water-splitting enzyme system; the electrons from photogenerator I reduce $NADP^+$ to NADPH *via* a series of enzyme reactions. The electrons produced by photogenerator II discharge in a series of dark reactions the holes formed at photogenerator I. In this reaction chain there is an electron pool (capacity 14 electrons per chain) in which at least 10 electron transport chains are interconnected.

3. Because of the anisotropic arrangement of the photogenerator poles perpendicular to the plane of the thylakoid membrane, the charge separation induced by light leads to the build-up of an electric field across the membrane. Utilization of the electrochromism effect enables the pigment molecules embedded into the thylakoid membrane to be used as molecular voltmeters and as molecular ammeters. In this way, after appropriate calibration, both the size of the fields and the kinetics of the induced ion flows can be measured[4].

4. Proton flow plays a role owing to participation of protonizable groups in electron transport systems. The kinetics of this flow were analyzed by means of indicators. In light a gradient of 3 to 4 pH units ($pH_{interior} < pH_{exterior}$) is built up over the thylakoid membrane[5].

5. The water-splitting enzyme system has the ability to store holes. H_2O is oxidized to O_2 only when four holes have been accumulated. The lifetime of the trapped holes depends on the state of accumulation and can be influenced by chemical reagents[6].

6. For the mechanism of energy conservation leading to the formation of ATP, it could be shown that the energy is stored primarily as an electrochemical potential across the thylakoid membrane. It is assumed that this potential induces an ion transfer (probably an H^+-flow) through a special enzyme system, the ATPase. In this way chemical reactions are started in the ATPase that lead to binding of phosphate to ADP[2]. Details of this mechanism are unknown.

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[1] *H. Rüppel* and *H. T. Witt*, Methods Enzym. *16*, 316 (1970).
[2] *H. T. Witt*, Quart. Rev. Biophys. *4*, 365 (1971).
[3] *Ch. Wolff*, Photochem. Photobiol., in press.
[4] *W. Junge* and *R. Schmid*, J. Membrane Biol. *4*, 179 (1971).
[5] *B. Rumberg* and *U. Siggel*, Naturwissenschaften *56*, 130 (1969).
[6] *G. Renger*, Physiol. Vegetale *10*, 329 (1972).

Structure and Function of Natural Proteinase Inhibitors

By *Harald Tschesche*[*]

Inhibition of proteolytic activities by proteinase inhibitors is one of the natural control mechanisms of enzymatic activity in the organism and is comparable with repression of enzyme synthesis at the DNA-RNA transcription level and with allosteric inhibition of completed enzymes. Proteolytic activities such as that of trypsin can be limited as to location and time either by permanent inhibitors such as the trypsin-kallicrein inhibitor from bovine organs[1] or temporarily[2] by, *e.g.*, the secretory trypsin inhibitors of mammalian pancreas. The enzymatic inactivation is due to a competitive inhibition with stoichiometric formation of a 1:1 molar complex C of enzyme T and inhibitor I or I*, which according to *Laskowski, Jr.*[3], occurs *via* a loose addition complex L or L*:

$$T + I \rightleftharpoons L \rightleftharpoons C \rightleftharpoons L^* \rightleftharpoons T + I^*$$

Figure 1 shows the complete covalent structure of the secretory trypsin inhibitor I from porcine pancreas[4]. It is characterized by a compact arrangement in which the active site (Lys^{18}-Ile^{19}) forms a "cyclic substrate" within a ring that is closed by a disulfide bridge, in accord with the hypothesis of *Ozawa* and *Laskowski, Jr.*[3]. The C-terminus is attached to the remainder of the molecule in a chain that runs parallel to the active site and contains the "potential breaking point" (Arg^{44}-Gln^{45}) for inactivation of the molecule during temporary inhibition. The

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inactivation is initiated by a partial proteolysis reaction at the reactive center with cleavage of the Lys^{18}-Ile^{19} bond to form a modified but still active inhibitor I*. Subsequent cleavage of the Arg^{44}-Gln^{45} bond inactivates the molecule. Therefore blocking of Arg^{44} against tryptic cleavage by butanedione holds up the inactivation by a factor of 25.

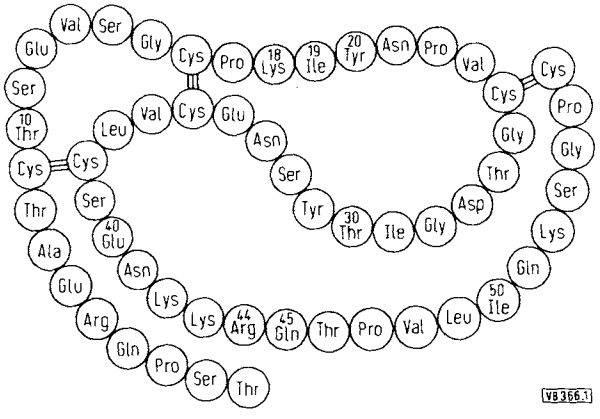

Fig. 1. Complete covalent structure of the porcine pancreatic secretory inhibitor I.

From the covalent structure we can conclude that the inactivation is made easier by the parallel courses of the polypeptide chains that contain, respectively, the active site and potential breaking point, since only a slight reorientation of the enzyme molecule in the loose addition complex L* from the active site to the potential breaking point is required. Comparison of the primary structures of the inhibitors from pig and sheep (also from ox[5]) shows that the C-terminal partial sequences (residues 44—56) rarely undergo mutation, thus underlining the importance of this portion of the molecule for the biological function of the whole.

The physiological role of the secretory pancreatic inhibitors is probably to be sought in prevention of premature zymogen-activation of the enzymatic digestive potential in the acinar cells or the duct of the gland. The mechanism of temporary inhibition later permits biological recovery of the inhibited enzyme.

This phenomenon of temporary inhibition is shown also by two isoinhibitors from mammalian sperm, in the inactivation of trypsin (from bovine and porcine pancreas)[6], which were first isolated in pure form from seminal plasma of the boar. The seminal inhibitor I contains 67 amino acids, galactosamine and glucosamine; in inhibitor II there are one lysine and one arginine residue less. The amino acid compositions and N-terminal sequences show that there is no homology between these two inhibitors secreted by the vesicular gland and the inhibitor secreted by the pancreas (Fig. 1). Besides a temporary inhibition of trypsin the two seminal inhibitors exhibit permanent inhibition of the egg-penetrating acrosin of boar sperm in a 1:1 stoichiometric reaction. This last-mentioned finding could be of special importance for the fertilizing capacity of sperm, *i.e.* for its attainment of fertilizing ability in the female genital tract and thus for its ability to penetrate the egg cell membrane (zona pellucida) which *in vivo* occurs with participation of acrosin[7, 8].

Lecture at Bonn (Germany) on January 9, 1973 [VB 366 IE]
German version: Angew. Chem. 85, 545 (1973)

[1] *R. Vogel, I. Trautschold,* and *E. Werle:* Natural Proteinase Inhibitors. Academic Press, New York 1968.

[2] *M. Laskowski, Sr.* and *F. C. Wu,* J. Biol. Chem. *204,* 797 (1953).

[3] *M. Laskowski, Jr.* and *R. W. Sealock* in *P. D. Boyer:* The Enzymes. Academic Press, New York 1971, p. 375; *K. Ozawa* and *M. Laskowski, Jr.,* J. Biol. Chem. *241,* 3955 (1966).

[4] *H. Tschesche, E. Wachter, S. Kupfer,* and *K. Niedermeier,* Hoppe-Seylers Z. Physiol. Chem. *350,* 1247 (1969); *H. Tschesche* and *E. Wachter,* Eur. J. Biochem. *16,* 187 (1970); *H. Tschesche, E. Wachter, S. Kupfer, R. Obermeier, G. Reidel, G. Haenisch,* and *M. Schneider* in *H. Fritz* and *H. Tschesche:* Proceedings International Research Conference on Proteinase Inhibitors. de Gruyter, Berlin 1971, p. 207; *D. C. Bartelt* and *L. J. Greene,* J. Biol. Chem. *246,* 2218 (1971); *H. Tschesche, M. Schneider, G. Reidel,* and *H. Klein,* Hoppe-Seylers Z. Physiol. Chem. *352,* 763 (1972).

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[7] *R. Stambaugh* and *J. Buckley,* J. Reprod. Fert. *19,* 423 (1969).

[8] *L. J. D. Zaneveld, K. L. Polakoski, R. T. Robertson,* and *W. L. Williams* in *H. Fritz* and *H. Tschesche:* Proceedings International Research Conference on Proteinase Inhibitors. de Gruyter, Berlin 1971, p. 236.

ABSTRACTS

Reviews

Abstracts of selected progress reports and review articles

The use of spectroscopic methods in the structural analysis of coal and petroleum is dealt with by *J. G. Speight.* The author considers UV, IR, NMR, mass, and ESR spectroscopy, as well as X-ray diffraction and electron microscopy. All these techniques furnish information on structural details of the two natural products, but so far it has not proved possible to combine these details into a comprehensive overall picture, not least owing to the chemical and physical (solubility problems) complexity of the mixtures designated coal and petroleum. The literature is covered up to August 1970. [The Application of Spectroscopic Techniques to the Structural Analysis of Coal and Petroleum. Appl. Spectrosc. Rev. *5,* 211—263 (1972); 306 references]

[Rd 571 IE—G]

Photochemistry in macromolecular systems is considered by *J. E. Guillet.* The photochemical reactions typical of

chromophoric groups in small organic molecules also occur in macromolecules. The most important ones are: photodimerization; photoisomerization; generation of free radicals; photocyclization; photorearrangement. Polymeric ketones are particularly suitable for obtaining an insight into such processes. Apart from the influence of viscosity, molecular weight, concentration, and chain mobility, particular importance attaches to intramolecular energy transfer. [Photochemistry in Macromolecular Systems. Naturwissenschaften *59*, 503—509 (1972); 23 references]

[Rd 605 IE—M]

Toxic proteins capable of inhibiting protein synthesis are considered by *S. Olsnes*. Thus Colicin E3 kills susceptible bacteria by inhibiting ribosome function. Diphtheria toxin blocks protein synthesis in eukaryotes by inactivating peptidyl transferase II. The plant toxins abrin and ricin probably also interfere with some of the processes necessary for elongation of the peptide chain. [Toxic Proteins Inhibiting Protein Synthesis. Naturwissenschaften *59*, 497—502 (1972); 82 references]

[Rd 607 IE—M]

Reductions of functional groups by sulfurated hydridoborates such as $NaBH_2S_3$ and their particular application to steroidal ketones are discussed by *J. M. Lalancette, A. Frêche, J. R. Brindle*, and *M. Laliberté*. Reagents of this type are readily accessible from hydridoborates and S, Se, or Te in *e. g.* THF, diglyme, or dioxane. Aldehydes and ketones are reduced to the alcohols at low temperatures and also to the disulfides at higher temperatures. Aromatic nitro groups can be reduced in a highly selective manner to amino groups. Reduction of the 3-oxo groups of steroidal ketones proceeds without attack of oxo groups at C-11, C-12, C-17, and C-20. [Reduction of Functional Groups with Sulfurated Borohydrides. Application to Steroidal Ketones. Synthesis *1972*, 526—532; 20 references]

[Rd 612 IE—M]

Spectroscopic studies on electron donor-acceptor systems are the topic of a review by *C. N. R. Rao, S. N. Bhat*, and *P. C. Dwivedi*. An introduction to the theory of such systems is followed by an account of their investigation by electronic, IR, Raman, NMR, and ESR spectroscopy. The article provides an exhaustive survey of the available literature (latest references from 1970) but the authors emphasize the need for a critical approach to many of the data considered. [Spectroscopy of Electron Donor-Acceptor Systems. Appl. Spectrosc. Rev. *5*, 1—170 (1972); 564 references]

[Rd 569 IE—G]

Hydrogenations and isomerizations over zinc oxide are the subject matter of an article authored by *R. J. Kokes* and *A. L. Dent*. The review deals with the active sites of the catalyst, the mechanism of ethylene hydrogenation, and reactions with propylene, butene, and acetylenes. It is seen that all the reactions listed can be considered in common terms if the active site is regarded as a metal-oxygen pair (*i.e.* a cation-anion pair) that can effect heterolytic cleavage of an acidic C—H bond. [Hydrogenation and Isomerization over Zinc Oxide. Advan. Catal. *22*, 1—50 (1972); 75 references]

[Rd 578 IE—G]

The nuclear magnetic resonance of molecules oriented in electric fields is considered in a survey penned by *C. W. Hilbers* and *C. MacLean*. They cite relevant literature up to 1971 and also report unpublished experimental results. The following topics are discussed: theory of NMR spectroscopy of oriented molecules; comparison of experimental results with theoretical predictions; dependence of the NMR spectrum on the angle between the molecules in a liquid; and relationships between the Kerr effect and the nuclear magnetic resonance in an electric field. [NMR of Molecules Oriented in Electric Fields. NMR *7*, 1—52 (1972); 50 references]

[Rd 573 IE—G]

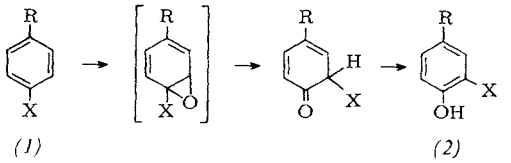
"Carboxypeptidase A: a mechanistic analysis" is the subject of review by *E. T. Kaiser* and *B. L. Kaiser*. Carboxypeptidase catalyzes the hydrolysis of peptides or esters of *N*-acyl α-amino acids and *O*-acyl α-hydroxy acids adjacent to the terminal COOH groups. One Zn^{2+} ion is required per molecule of enzyme. The mode of action of the enzyme is deduced by the authors from the results of kinetic findings, studies of structure-reactivity relationships, and pH dependence in reactions with synthetic substrates, as well as from the experimental results. Arg^+-145, Glu-270, and a molecule of water bound to zinc participate directly in the process. [Carboxypeptidase A: a Mechanistic Analysis. Accounts Chem. Res. *5*, 219—224 (1972); 43 references]

[Rd 601 IE—L]

The application of phenolic oxidation to the total synthesis of isoquinoline- and related alkaloids in the subject of a report by *T. Kametani* and *K. Fukumoto*. The term phenolic oxidation denotes the oxidative radical coupling between the phenolic O atom or a C atom (*ortho* or *para* to the OH group) and a corresponding atom of another phenol to give C—O and C—C bonds. This mode of reaction is of considerable significance for the biosynthesis of numerous natural products; it can frequently be imitated in the laboratory with the aid of oxidizing agents such as $FeCl_3$ and $K_3[Fe(CN)_6]$. [Application of Phenolic Oxidation to the Total Syntheses of the Isoquinoline and Related Alkaloids; Biogenetic Type Synthesis. Synthesis *1972*, 657—674; 106 references]

[Rd 603 IE—M]

The significance of arene oxides and the NIH shift in metabolism, toxicity, and carcogenicity of aromatic compounds is discussed by *J. W. Daly, D. M. Jerina*, and *B. Witkop*. The primary products of aromatic substrates are arene oxides which undergo conversion into, *e. g.*, dihydro diols (by spontaneous isomerization into phenols). Introduction of the OH group by monooxygenases is accompanied by a migration [*(1)→(2)*] of the original substituent



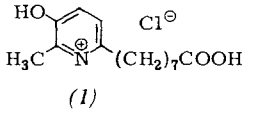
(1) *(2)*

(usually H, less frequently CH_3 or halogen), *i.e.* the NIH shift. The toxicity of aromatic pharmaceuticals and the

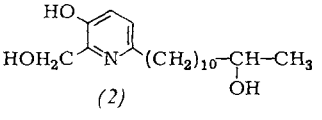
carcinogenic action of polycyclic aromatic hydrocarbons have been shown in model experiments to be interpretable in terms of arene oxide opening by nucleophilic groups present in tissues and covalent binding to biopolymers. [Arene Oxides and the NIH Shift: The Metabolism, Toxicity and Carcinogenicity of Aromatic Compounds. Experientia *28*, 1129—1264 (1972); 189 references]

[Rd 604 IE—M]

Syntheses of carpyrinic acid *(1)* and related pyridines having long aliphatic chains are discussed by *G. Fodor, J.-P. Fumeaux*, and *V. Sankaran*. Compound *(1)* is a key intermediate in the synthesis of alkaloids bearing piperidine groups and such long chains. The authors give four synthetic



(1)



(2)

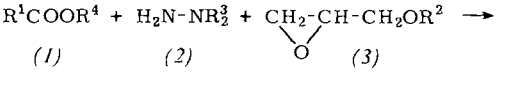
routes to *(1)*. The synthesis of dehydroprosopine *(2)*, an important intermediate in the total synthesis of prosopine and prosopinine, is reported. The article also gives an account of the synthesis of fire ant venoms (2-methyl-6-alkyl- and alkenylpyridines). [Syntheses of Carpyrinic Acid and of Related Pyridines with Long Aliphatic Chains. Synthesis *1972*, 464—472; 34 references]

[Rd 613 IE—M]

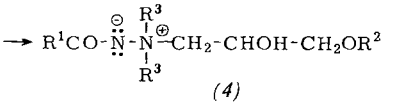
Patents

Abstracts of selected "Deutsche Offenlegungsschriften" (DOS), *i. e.* provisionally published specifications as filed with the German Patent Office

New surface active ammonioamidates *(4)* with long-chain ether residues on the quaternary nitrogen atom can be prepared by heating equimolar quantities of carboxylic esters *(1)*, dialkylhydrazines *(2)*, and glycidyl ethers *(3)* at 60—80°C. For example, from 15 g of *N,N*-dimethylhydrazine, 60.5 g of dodecyl glycidyl ether, and 18.5 g of



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



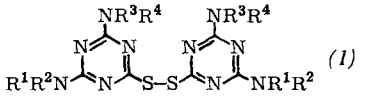
(4)

R^1 = H, CH_3, C_2H_5; R^2 = aliphatic residue (C_8—C_{18}), preferably linear with an even number of C atoms, which may be saturated or unsaturated; R^3 = CH_3, C_2H_5; R^4 = alkyl (C_1—C_4)

methyl acetate in 100 ml of butanol at 60°C, one obtains *N,N*-dimethyl-*N*-(2-hydroxy-3-dodecyloxypropyl)ammonioacetamidate. The ammonioamidates have an excellent washing and cleaning action, particularly below 60°C, and are therefore suitable for use as components in cold washing products for wool or fully synthetic textiles. The ability to disperse calcium soaps is good. Some of the compounds, *e.g. (4)* with $R^1 = C_2H_5$, $R^2 = C_{12}H_{25}$, and $R^3 = CH_3$, are characterized by low foaming power, and can therefore be used in particular for machine-wash detergents. [DOS 2059289; Henkel & Cie GmbH, Düsseldorf]

[PR 80 IE—V]

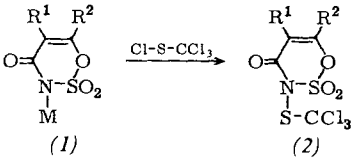
A mixed accelerator for the vulcanization of natural and synthetic rubbers based on halogen-free dienes consists of a) bis(1,3,5-triazinyl) disulfides *(1)* in which one of the residues R^1—R^4 is hydrogen and the others are identical or different, linear or branched alkyl groups (C_1—C_4), b) a mercapto accelerator, and possibly c) a thiuram accelerator. The use of the mixture avoids the disadvantage of the long heating time required when compounds *(1)* are used alone; the high stress values of the vulcanized products are not impaired. [DOS 2109244; Degussa, Frankfurt; Bayer, Leverkusen]



(1)

[PR 98 IE—E]

New *N*-trichloromethylthiooxathiazinones *(2)* are obtained by reaction of metal salts of oxathiazinones *(1)* with trichloromethylsulfenyl chloride between 0°C and the boiling

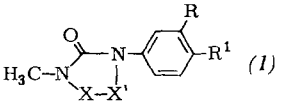


(1) *(2)*

point of the solvent (apolar or polar). The oxathiazinones *(2)* can be used against fungus diseases of cultivated plants. [DOS 2059249; Farbwerke Hoechst AG; Frankfurt/Main-Höchst]

[PR 100 IE—N]

Aminoimidazolidinediones and iminoimidazolidinediones *(1)* exhibit a primarily herbicidal but also fungicidal and



(1)

R = H, Cl, CH_3; R^1 = H, Cl, Br, SCH_3; X or X': >CO; X' or X: >C=N—R^2, >CH—NH—R^2; R^2 = H, substituted phenyl, other (substituted) substituents

bactericidal action. They can be obtained by several known methods. [DOS 2107146; C. H. Boehringer Sohn, Ingelheim]

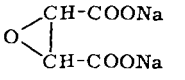
[PR 106 IE—N]

High molecular weight, fully aromatic copolyamide-phosphonamides, which can be made into filaments, fibers, and sheets and used for the production *e.g.* of high-temperature electrical insulators, flame-resistant protective clothing, parachutes, and fuel containers, can be prepared by addition of a phosphonic dihalide, *e.g.* phenylphosphonic

dichloride, to a melt of at least one excess aromatic diamine, *e.g. m*-phenylenediamine, at a high temperature. After the reaction, the product is dissolved in a conventional solvent for aromatic polyamides, such as dimethylacetamide or *N*-methyl-2-pyrrolidone, at least one aromatic dicarboxylic acid halide, *e.g.* isophthaloyl chloride, is added to this solution between 0 and −20 °C, and the mixture is polycondensed to completion at this temperature to obtain a high molecular weight product. [DOS 2062774; Farbwerke Hoechst AG, Frankfurt/Main-Höchst]

[PR 58 IE—O]

The *cis* isomer of disodium epoxysuccinate *(1)* can take the place of sodium tripolyphosphate, which has until now been extensively used as a builder in detergents and cleaning mixtures, but which should no longer be used because of its adverse effect on bodies of water. Since *(1)* contains no



(1)

plant nutrients such as phosphorus or nitrogen, unlike polyphosphate, it has no eutrophic effect on fresh-water flora, and in particular it does not lead to excessive growth of algae. The natural development of the fauna and flora of the water bodies is not disturbed by *(1)*, so that the detergents present in washing agents can be biologically degraded. 20—45 wt.% of the detergent mixture consists of alkaline sodium salts, of which 40—85 wt.% preferably consists of *(1)*. The full action of *(1)* is achieved in washing baths at pH 9. *(1)* has sufficient thermal stability for use at normal washing temperatures. Its prime cost is very little above the cost of tripolyphosphate. *(1)* is prepared by epoxidation of maleic acid with 30% H_2O_2 at 60 °C in aqueous solution in the presence of sodium tungstate. [DOS 2160908; Produits Chimiques Pechiney-Saint-Gobain, Paris]

[PR 81 IE—V]

To prepare *N*-disubstituted glycines, amino alcohols such as triethanolamine are oxidized with O_2 in the presence of Pt, possibly on a catalyst support and possibly in the presence of a solvent at 25—110 °C. The glycines obtained in this way are used for organic syntheses, as textile auxiliaries, and particularly as builders for detergents. [DOS 2103724; Chemische Werke Hüls, Marl]

[PR 110 IE—B]

BOOK REVIEWS

Elektronenanlagerungs-Massenspektrographie organischer Substanzen (Electron Addition Mass Spectrography of Organic Substances). By *M. von Ardenne, K. Steinfelder,* and *R. Tümmler*. Springer-Verlag, Berlin-Heidelberg-New York 1971. 1st ed., viii, 403 pp., 109 figs., stitched DM 68.—.

The present book sums up several years' work by the authors in the development and application of electron addition (EA) mass spectrography in the Manfred von Ardenne Research Institute, Dresden.

The fundamentals of the method are presented in the first part of the book, and are followed by a description of the equipment and general questions of sample preparation, measuring technique, and evaluation of the spectra. After a discussion of the ionization mechanisms, there is a short comparison of the EA mass spectra of negative and positive ions.

In the second part of the book, after dealing with a number of possible applications, mainly in the chemistry of natural products, the authors present a clear description of the classes of substances that have been investigated so far and of the decomposition rules that have been explained. The book ends with extensive tables containing the EA mass-spectroscopic data known at present.

The book should be equally valuable to the advanced chemist and to the specialist in the field of mass spectrometry. As an additional method, EA mass spectrography will undoubtedly find much more frequent use in analytical chemistry in the future for the solution of special problems, despite the need for larger samples than in electron bombardment mass spectrometry.

Gerd Remberg [NB 136 IE]

Real-Lexikon der Medizin (Encyclopedia of Medicine). 6 volumes in a loose-leaf system. Edited by *G. Thiele* and *H. Walter*. Urban & Schwarzenberg, München. Vol. 3 (F-Hyperl) 1969/70, ii, 804 pp., 140.— DM. Vol. 4 (Hyperm—Melusinidae) 1971/72, viii, 802 pp., numerous figures and tables, 160.— DM.

Two thirds of the encyclopedia[*] have now been completed. They show that the work is not only important for doctors, but will be of use also (and perhaps especially) to those who have a sort of scientific point of contact with medicine on the chemical side. Its content is lexical in the best sense, *i.e.* for each concept one not only finds a definition, but also learns something about the factors that make the object in question or the associated phenomenon important in medicine. In some cases, however, the necessary conciseness of expression leads to impenetrable brevity, which makes the explanation understandable only to those who are already fundamentally in possession of the information, but which may nevertheless serve as an indication to the novice that he still has something to learn here (as under the keyword "gamma globulins"). A literature reference to open the door to further studies would have been useful in this connection, but perhaps this is too

[*] Cf. Angew. Chem. internat. Edit. *8*, 222 (1969).

much to ask. There are interesting things to be learnt in this book, *e.g.* that "ammonium carbonicum" (why not ammonium carbonate?) is also known as "Geistersalz", or that 2,6-lupetidine is not described in medical (or rather pharmaceutical) circles as 2,6-dimethylpiperidine, but is known by the grander-sounding name "nanofinum". This is not necessarily the editors' fault, but at the same time it does not contribute much to a mutual understanding between different scientific disciplines. However, the chemist will welcome the clear and detailed schemes of important metabolic processes. On the whole, we have here a work that is outstanding for the care with which it has been edited, and that will be of great value to its owner (not least because of the inclusion of English and French equivalents of numerous keywords).

Helmut Grünewald [NB 130 IE]

Handbuch des kathodischen Korrosionsschutzes [Handbook of Cathodic Corrosion Protection]. By *W. v. Baeckmann* and *W. Schwenk*. Verlag Chemie GmbH, Weinheim/Bergstr. 1971, 1st ed., xxii, 422 pp., 204 figs., 53 tables, cloth DM 140.—.

Mainly in connection with the growing use of underground pipelines for petroleum and petroleum products, water, and natural gas and the steadily expanding use of underground cable systems, cathodic corrosion prevention has developed into a branch on a par with protection by surface coatings *etc.* More than in any other branch of corrosion prevention, precise knowledge of the electrochemical principles is essential to success here, since currents and potentials are used to intervene in the corrosion process; the effects can be determined much more accurately than *e.g.* those of a process that takes place over a long period, such as the diffusion of electrolytes.

The present book presents, for the first time in German, a comprehensive treatment of the entire field of cathodic and anodic corrosion protection, and the mathematical formulas collected in the Appendix show the importance of the calculations. Since no calculation is possible without the results of measurements, a chapter on general measuring techniques is included; the problems of measurement must be considered at the planning stage, and repeated check measurements are also necessary later.

The range of problems that can be solved with the aid of cathodic protection will be appreciated even from the following incomplete list of objects that can be successfully protected: pipelines, storage tanks, telephone cables, power cables, ships, steel constructions in sea water, and underground plants, and also the protection of specific objects such as hot-water systems and cold-water systems. The possibility of calculation also allows a fairly accurate estimate of costs (installation costs, operating current costs, maintenance costs, anode consumption, *etc.*).

The book, which represents the sum total of existing knowledge, should remain the standard work for a long time. Finally, a survey of correct terminology is presented; a side effect may be that this will be used by other authors in the future. Despite its high price, it is to be hoped that this book will reach the widest possible circle of readers.

Herbert Puschmann [NB 152 IE]

Gmelins Handbuch der anorganischen Chemie (Gmelin's Handbook of Inorganic Chemistry). 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. 8th fully revised Edition.

System No. 49: Niobium, Part B 3. Oxoniobates (excluding alkali metal niobates). Editor: *Herbert Lehl.* Compiled by *Hartmut Bergmann.* 1971. vi, xxii, 330 pp., 205 figures, Balacron DM 411.—.

The third volume of Part B, which was started in 1970[1], deals with oxoniobates, from those of the alkaline earth metals to those of vanadium. The importance of this class of compounds can be seen from the mere size of the volume, which covers the literature up to 1970. This is due to the special electrical and optical properties of the oxoniobates which are playing an increasingly important role both in industry and in science. Polycrystalline preparations are often prepared by heat treatment of oxide mixtures or of simultaneously precipitated oxide hydrates and of mixtures of the carbonates or oxalates, as well as by heating niobium with metal oxides or by oxidation of niobium alloys. The equilibrium diagrams of the systems have been very thoroughly investigated in many cases with the aid of X-ray and thermoanalytical methods. Many products of the systems discussed have found practical use, examples being the "PZT piezoceramics". These consist of $Pb(Zr,Ti)O_3$ modified with Nb_2O_5 and other oxides, and have advantages in respect of temperature resistance and aging resistance over the $BaTiO_3$ piezoceramics in electromechanical transducers. The volume contains very many figures showing equilibrium diagrams, lattice structures, and temperature dependence of dielectric constants, elastic coefficients, piezoelectric constants, and other parameters of ceramic preparations. The last section of the volume, "Definition and General Literature", would have been better placed at the beginning, though it is referred to there, together with the remark that the alkali metal niobates are discussed in "Niobium" volume B4, which is to be published in 1972, and will complete System No. 49.

System No. 47: Lead, Part B1. The element (excluding electrochemical behavior). Principal editor: *Anna Bohne-Neuber.* 1972. vi, xx, 497 pp., 87 figures, Balacron DM 596.—.

Whereas Part C of System No. 47 (Lead), which was published in 1969—1971[2], dealt with the metallurgy, alloys, and compounds of lead, the present first volume of Part B is concerned with the element. The second volume will be devoted to the electrochemistry of lead.

The present volume first describes the abundance, preparation, enrichment, separation, and properties of the numerous lead isotopes. As a result of accurate atomic weight determinations, it has recently become necessary, as for many other elements, to limit the accuracy formerly aimed at and claimed for the atomic weight, since the fluctuations of the isotope abundances, which are considerable even for ordinary lead, are much greater still for the naturally occurring radiogenic leads. The most recent value for the atomic weight of lead on the ^{12}C scale is 207.2. After a short chapter on the properties of the nuclides (nuclide masses, nuclear moments, excitation, decay), the properties of the atom and of the atom-ions (both the free atom-ions and the Pb^{2+} ions in crystals and solutions) are described. Pb^{3+} ions exist in crystals. Considerable space is devoted to the description of the crystallographic properties of lead, which also deals with

its deformation and softening. The description of the mechanical, thermal, magnetic, electrical, and optical properties is also very extensive (almost 100 pages), in agreement with its industrial importance.

The second part of the volume is devoted to the chemical behavior of the metal and of lead ions in solution. The divers uses of lead in the chemical industry are mainly based on its chemical resistance to sulfuric acid and the ease with which it is shaped. The chapter "Detection and Determination" is very detailed. Though the data on the determination and separation methods are confined to the more recent secondary literature and the principal monographs since 1950 [apart from this the reader is referred to the Handbuch der analytischen Chemie (Handbook of Analytical Chemistry) edited by *W. Fresenius* and *G. Jander*], the list of the most important recent literature since 1950 on general detection methods and detection and determination in special cases occupies about 100 pages.

A chapter entitled "Toxicity", which deals with lead poisoning by foodstuffs, lead in the air, and water containing lead, the manner in which lead acts in the body, and diagnosis and therapy, completes the volume, which will certainly be of interest to others besides chemists. Physicists, metallographers, metallurgists, the lead-processing industry, and toxicologists will also find it a rich source of information. The literature is covered up to and in some cases beyond the end of 1969.

System No. 47: Lead B 2. The element (electrochemical behavior). Editor: *Gerhart Hantke.* 1972. vi, xiv, 416 pp., 173 figures, Balacron DM 505.—.

With a lapse of only a few months since the appearance of Part B 1 of System No. 47, Lead, Part B 2 has now also been published. This volume deals with the electrochemical behavior, which was excluded from the first volume.

The great interest and the consequent intensive studies that have been devoted to the electrochemical properties of lead have their origin in its fields of use. A thorough knowledge of the electrochemical behavior is demanded on the one hand by the large-scale use of lead in the lead accumulator for the storage of electricity, and on the other by lead coating for the production of accumulator plates or for the protection of other metals against corrosion, or by electrolytic deposition for the refining of lead.

The data on the lead accumulator are confined in the present volume to a bibliography, which contains only the monographs and reviews on this subject. The discussion of electrolytic deposition, on the other hand, occupies almost half of the volume (188 pages). The chapter deals in detail with the deposition of lead from aqueous and non-aqueous solutions, from suspensions, and from melts. Lead can even be deposited electrolytically from solid lead compounds. The remainder of the volume is divided into the chapters: Standard potential; Electrolytic solution pressure; Ionic mobility; Potentials; Electrokinetics; Cathodic hydrogen overpotential; Oxygen overpotential; Behavior as an electrode; Behavior as a cathode; Behavior as an anode.

The material is arranged well. Though the literature is fully evaluated only up to the end of 1968, numerous important later reports are also covered. Chemists will be disturbed by a series of faults in terminology, only a few of which will be mentioned here. On p. 25, phosphoric acid and its primary, secondary, and tertiary sodium salts are referred to as "PO_4 compounds". It would also have been more accurate, in Section 11.3.37 (pp. 370—380), to use either the name diphosphate or the correct formula $P_2O_7^{4-}$ instead of P_2O_7. The authors are equally free with ionic charges in Section 11.3.33 (pp. 360—370), in which the correct formula $PbSiF_6$ and the incorrect formula $Pb(SiF_6)_2$ appear to be randomly distributed both in the marginal headings and in the text. The description "natronalkalisch" (roughly equivalent to "soda-alkaline") *e.g.* on pp. 384 and 386, is unfortunate, since its meaning is unclear, particularly to foreign users of the volume. It would also have been better, in view of the world-wide readership, to use the internationally accepted abbreviation EDTA (which is also used by *G. Schwarzenbach*) instead of ädt (p. 348) for ethylenediaminetetraacetic acid and its anions. The inclusion of lead thiocyanate among the lead cyanide compounds (p. 23) is wrong.

Despite many minor faults of the type mentioned, the volume is an important source of information, which offers an encyclopedic description of the electrochemical behavior of lead, *i.e.* properties of this metal that are in daily use by nearly every one of us, and that form the basis of an entire industry.

Ekkehard Fluck [NB 115 IE]

[1] Cf. Angew. Chem. internat. Edit. *12*, 87 (1973).

[2] Cf. Angew. Chem. internat. Edit. *11*, 548 (1972).

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Extrachromosomal DNA in Bacteria

By Werner Goebel[*]

In addition to chromosomal DNA carrying the genetic information of the cell, many bacterial cells contain smaller circular DNA factors known as plasmids or episomes. These genetic elements endow the cell with additional biochemical capabilities. The fertility factors (F and F'), the antibiotic resistance factors (R), the colicinogenic factors (Col), the hemolytic factors (Hly), and other extrachromosomal DNA systems are described. These small DNA molecules can be isolated, and are therefore particularly suitable for the investigation of DNA replication and the stable establishment of genetic material in the bacterial cell.

1. Introduction

Deoxyribonucleic acid (DNA) contains the genetic information of every cell that is capable of division, and so determines the biochemical capabilities of the cell. Whereas the DNA of higher organisms (eukaryotic cells) is contained in the cell nucleus in the complicated structure of the chromosome[1], that of the bacterial cell exists in a "free" form (prokaryotic cells), presumably bound to the cell membrane[2]. Though bacteria have no chromosomes, bacterial DNA is frequently also referred to as chromosomal DNA. The information contained in the base sequence of the DNA (genetic code)[3] is transcribed into messenger ribonucleic acid (m-RNA) by RNA polymerase[4]. The information of the m-RNA is translated into proteins on the ribosomes[5] in a complicated but now largely understood process[6]. These proteins catalyze the chemical processes in the cell if they are enzymes, and contribute to the construction of the cell if they are structural proteins.

Unless the chromosomal DNA of the cell is modified by spontaneous mutations or by mutations induced by chemicals, UV radiation, *etc.*, the genetic information and hence the biochemical capabilities of the cell remain constant. All the cells of one type of bacterium should therefore exhibit exactly the same behavior. It is found, however, that individuals possessing additional biochemical capabilities occasionally appear: some *E. coli* cells can grow in the presence of one or more antibiotics, others release proteins that have a bactericidal action on other *E. coli* bacteria, and so on. These additional properties differ from chromosomal characteristics in the following respects: They can, albeit very rarely, spontaneously segregate on cell division. They can be eliminated by treatment with agents such as acridine orange[7], ethidium bromide[8], and sodium dodecyl sulfate[9]. Conversely, they can be transferred in many cases by cell contact to other bacteria that previously did not possess these characteristics.

It is now known that these properties are not determined by the chromosomal DNA but by additional DNA elements that are physically separate from the chromosomal DNA in the bacterial cell and are therefore known as "extrachromosomal DNA elements" or as "episomes" or "plasmids"[10]. These additional genetic elements can give the cell decisive selectional advantages under special growth conditions. However, a bacterial cell is not dependent on these plasmids, which are therefore described as "non-essential".

The purpose of the present article is to provide a general picture of the variety of these extrachromosomal DNA

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systems in bacteria. Special emphasis is placed on the physiological importance of these additional genetic elements to the bacterial cell and on their biochemical properties. Since the literature in this field has become very extensive, only a selection can be offered here (for reviews see[10-13]).

2. The Fertility or Sex Factor (F) of *Escherichia coli*

The first observation to suggest that bacterial DNA can be transferred from one bacterial cell to another was made by *Lederberg* for the intestinal bacterium *Escherichia coli*[14]. In this process, known as "conjugation", two bacterial cells come together, one of these being described as the male or donor cell and the other as the female or recipient cell. The process is determined by an extrachromosomal DNA element, the F (fertility) or sex factor. Through this F DNA, characteristics that are essential for conjugation become pronounced. The F^+ cell (male cell) forms specific cell wall appendages, which are known as sex pili or F pili (Fig. 1). Through these, contact is made with the female F^- bacterium. It is not yet certain whether the F pili are also involved in the transfer of the DNA.

The F pili have two properties: They confer a new antigen property upon the male bacterial cell[15] and they are specific receptors for certain bacteriophages[16].

During the conjugation, the extrachromosomal F DNA is transferred at a high rate ($\approx 100\%$) from the male to the female cell; chromosomal genes may occasionally also be transferred. The transfer of the F DNA presumably takes place by the "rolling-circle mechanism" illustrated in Figure 2. In this mechanism, one of the two strands of the plasmid DNA is forced out of the donor cell into the recipient cell. The complementary DNA strand is formed inside the recipient cell. The complementary strand to the DNA strand retained in the donor cell is also replicated[17,18].

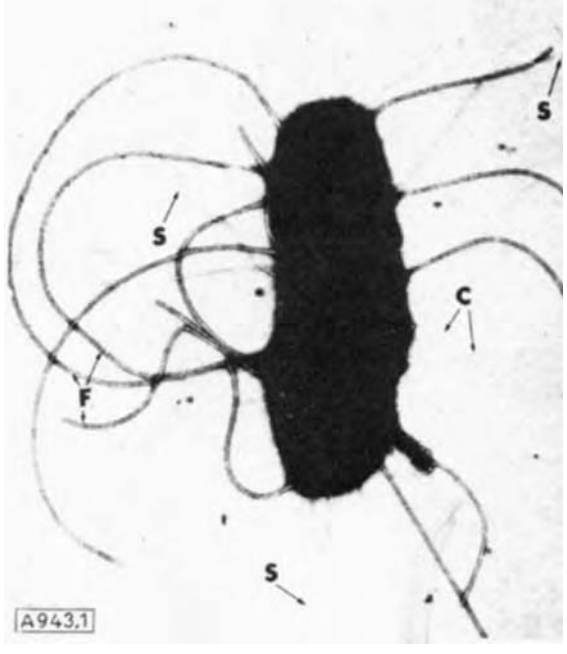

Fig. 1. Male F^- cell of *Escherichia coli* (after [7]). S = sex or F pili, C = normal pili, F = flagella. Magnification approx. 2500×.

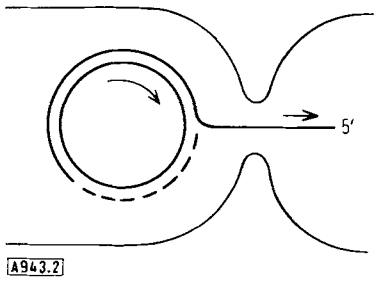

Fig. 2. Rolling circle model for the transfer of plasmid DNA during conjugation. The heavy DNA strand of the extrachromosomal factor unrolls on the covalently closed complementary light strand and is pushed through a plasma bridge (F pilus?) into the recipient cell. The synthesis of the complementary DNA strand takes place in the recipient cell (after [17,18]).

The F DNA may occasionally be integrated into the chromosomal DNA of the bacterium[19], and is then a covalently bonded component (Fig. 3). In this Hfr state

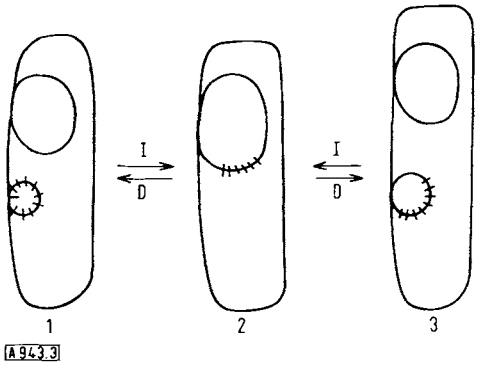

Fig. 3. Integration (I) and dissociation (D) of the F factor. 1) Male (F^+) cell, autonomous F state; top: chromosome, bottom: F factor. 2) The integration of the F DNA into the chromosomal DNA leads to the Hfr state. Dissociation can lead either back to the original state (1) or to the formation of an F' factor. 3) Male (F') cell, autonomous F' state. The F' factor carries a section of the chromosomal DNA in addition to the F DNA.

(Hfr = high frequency of recombinants), the male cell has the ability to transfer also the chromosomal DNA, in part or in whole, to a recipient cell during conjugation.

By dissociation, the F DNA can return from the integrated Hfr state to the autonomous extrachromosomal F^+ state. During this process, the F factor may occasionally take with it sections of the chromosomal DNA[20]. This results in the formation of F' factors (Fig. 3), which, in addition to the F properties (*e.g.* pilus formation, phage-specificity, transfer properties), also possess chromosomal characteristics. Thus the F' lac factor possesses all the genes required for the construction and regulation of the enzymes for the degradation of lactose. F' gal, in addition to the F properties, also encodes all enzymes for the degradation of galactose.

The F factor and some F' factors have now been isolated by methods discussed in Section 9. They are large circular DNA molecules.

On the basis of the rate of conversion of "supercoiled" F DNA into open-circular F DNA (see Section 9) by X-rays, *Freifelder* obtained a molecular weight of 45×10^6 daltons (D) for F DNA and 51×10^6 to 81×10^6 D for

F′ DNAs[21]. Other workers, who used mainly electron microscopy and sedimentation analysis for the determination of the molecular weight of F DNA, found a value of 62×10^6 D[22]. F′ factors, as one might expect, are larger. Careful measurements have given a molecular weight of 107×10^6 D for the F′ factor F′-Col V-Col B-trp-cys[23], which, in addition to the F DNA, carries the colicinogenic factors Col V and Col B (see Section 5) and the genes for the enzymes of the tryptophan and cysteine biosyntheses. F′ lac DNA has a molecular weight of 130×10^6 D according to sedimentation analysis. The number of F and F′ factors in the *E. coli* cell is small, and cannot be more than one or two copies per bacterial cell[24].

3. Antibiotic Resistance Factors (R) of Enterobacteria

Extrachromosomal DNA factors that have attracted special attention because of their potential danger to man are the antibiotic resistance factors or R factors. The phenomenon of transferable multiple antibiotic resistance in enterobacteria was first described by *Watanabe*[25,26], and is connected with the occurrence of R factors. Like the F and F′ factors these possess fertility and transfer properties, and can thus transfer the characteristic of multiple antibiotic resistance to suitable recipients by conjugation. The recipient cells for the transfer of R factors are mainly the bacteria belonging to the class of Enterobacteriaceae. The best-known of these is the generally harmless intestinal bacterium *Escherichia coli*. However, they also include bacteria that must be regarded as decidedly pathogenic, such as *Salmonella typhimurium*, which causes gastroenteritis, *S. typhi*, the agent responsible for typhoid, and *S. paratyphi*, the agent that causes paratyphoid, as well as the strains of *Shigella* that must also be considered as pathogenic enterobacteria (*e.g. Shigella dysenteriae*, which causes dysentery and severe diarrhea). These diseases, which are generally referred to as salmonelloses and shigelloses, may be endemic. It has already been seen in some cases how dangerous the course of these diseases can be if the pathogens carry R factors (Table 1).

In addition to the enterobacteria, *Pseudomonas* species, *Pasteurella* strains (*e.g. Pasteurella pestis*, the plague pathogen), and *Vibrio* strains (*e.g. Vibrio cholerae*, the cholera pathogen) can also act as recipients for R factors *in vitro*[28,29]. However, recent investigations on *Vibrio cholerae* strains carrying R factors have shown that with one exception (R ts 1 factor), all transferred R factors are unstable in this host and segregate after a few generations[30].

In addition to enterobacteria, naturally occurring *Pseudomonas* strains with R factors have also been isolated[31,32]. As a result of the intensive use of antibiotics in medicine and in animal feeding, antibiotic-resistant enterobacteria are now very widespread[10]. Under laboratory conditions, the R factors can be transferred with different probabilities to all known recipients; relatively little is known about the frequency of the transfer of R factors from one bacterial cell to another in the human or animal organism[33]. It cannot be ruled out in principle, however, that *Escherichia coli* having R factors could transfer multiple antibiotic resistance to salmonellae or shigellae *e.g.* in the human intestinal tract. Even a low transfer frequency in this direction can have a serious effect if antibiotics are in use at the same time, since under this selection pressure, only the antibiotic-resistant salmonellae or shigellae survive.

R factors are nowadays divided into two groups according to their effect on the F factor; these groups are designated as Rfi$^+$-factors and Rfi$^-$-factors.

If Rfi$^+$-factors are transferred to an F$^+$ strain, the F properties such as pilus formation and the ability to conjugate and to transfer are inhibited (fi$^+$ = "fertility inhibition" positive)[34,35]. The DNA of such R factors is assumed to code for a cytoplasmic repressor, which can also act on F DNA. Rfi$^-$-factors, on the other hand, do not inhibit the F properties on transfer to an F$^+$ strain. However, they can inhibit the pilus formation and the transferability of the fertility factor Col I (see Section 5).

It has been possible to show in some cases that the complete R factor consists of two DNA sections, which are known as the resistance (R) determinant and the resistance transfer factor (RTF). Thus in the transfer of R factors from R$^+$-*E. coli* bacteria to the enterobacterium *Proteus mirabilis*, the initially uniform R DNA dissociates into two distinguishable circular DNA molecules[36,37] (Figs. 4 and 5). The smaller DNA molecule ($MW = 10 \times 10^6 - 12 \times 10^6$ D) has the properties of the R determinant. It confers multiple

Table 1. Detection of salmonellae carrying R factors in four epidemics (modified after [27]). A = ampicillin, S = streptomycin, K = kanamycin, C = chloramphenicol, T = tetracycline, Su = sulfonamides.

Strain	Location of epidemic	Duration of epidemic	R factors detected with following resistances	% of resistant strains	Frequency of transfer to sensitive *E. coli* in 24 h
S. Oranienburg R-4-5	Paris	1963—1968	ASKCTSu	66	10^{-3}
			SKCTSu	17	10^{-2}
			AS	3	10^{-1}
S. Derby R 7	Lyon	1963—1964	ASK TSu	30	10^{-1}
			AS TSu	10	10^{-1}
			A	3	10^{-1}
S. Panama R 11	Paris	1965—1968	A K T	24	10^{-1}
			A T	32	10^{-1}
			A	3	10^{-1}
S. Stanleyville R 32	Dakar	1966—1967	ASKCTSu	78	10^{-4}

antibiotic resistance, but has no transfer properties. Bacterial cells that contain this plasmid are resistant to antibiotics, but they cannot transfer this resistance further. The larger DNA molecule (MW 55×10^6 D) is presumably the RTF portion. It possesses transfer properties, but does not confer any resistance to antibiotics. Bacterial cells that contain only this plasmid are no longer resistant to antibiotics, but can transfer this plasmid to recipient cells in the same way as F^+ bacteria.

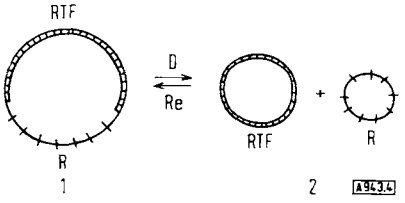

Fig. 4. Dissociation (D) of a complete R factor (1) into an RTF part and an R determinant (2), and recombination (Re).

The DNA of the R determinant contains genes that code for the production of specific antibiotic-inactivating enzymes. Chloramphenicol is inactivated by an R-specific acetylase[38,39], which can acetylate the antibiotic on the hydroxyl group of the side chain (Fig. 6). R-specific enzymes have also been detected for the inactivation of ampicillin (β-lactamase), streptomycin (phosphorylase), neomycin, and kanamycin (acetylases)[40-42]. Resistance to tetracyclines and sulfonamides results from the inhibition of their uptake caused by R factors[43,44]. The molecular nature of this permeability barrier is not yet known. The extent of this multiple antibiotic resistance produced by R factors depends on the number of resistance genes and hence on the number of inactivating enzymes. An R factor can thus give a cell transferable resistance to a single antibiotic (*e.g.* tetracycline) or to six or more antibiotics at the same time *e.g.* chloramphenicol, streptomycin, ampicillin, sulfonamides, neomycin, kanamycin, *etc.*).

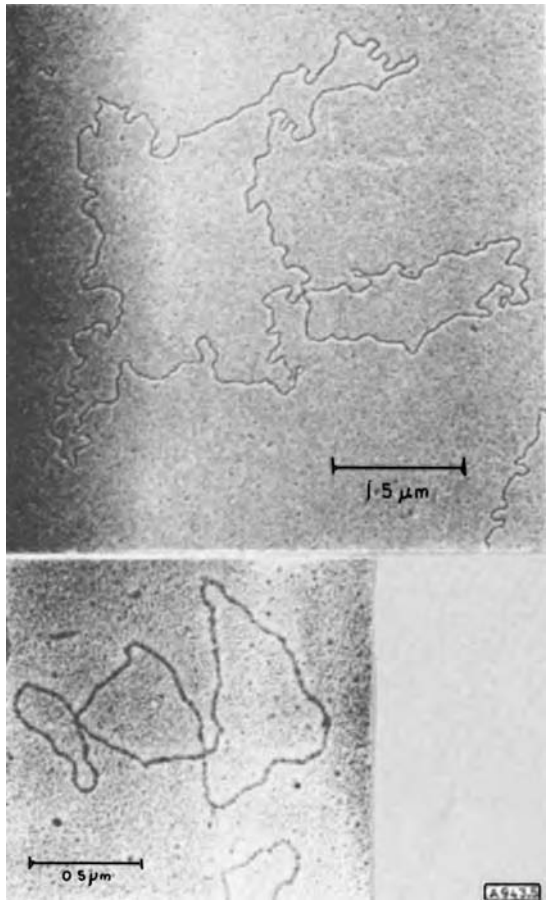

Fig. 5. Electron micrograph of DNA molecules after dissociation of an R factor into the RTF part (upper photograph) and the R determinant (lower photograph) on transfer in *Proteus mirabilis* (after [37]).

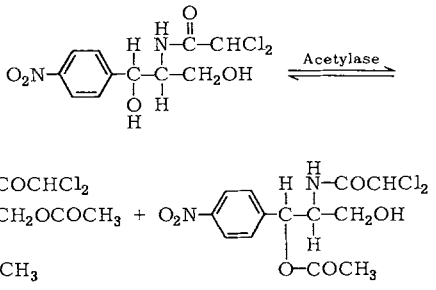

Fig. 6. Inactivation of chloramphenicol by the acetylase determined by an R factor.

4. Penicillinase Plasmids of Staphylococci

Penicillin-resistant strains of staphylococci are widespread. This resistance is due to the occurrence of the "penicillinase plasmids", whose molecular properties have been investigated in particular by *Novick* and by *M. H. Richmond* in *S. aureus*[45,46]. These penicillinase plasmids are a class of extrachromosomal DNA elements that resemble the portion of the R factors known as the resistance (R) determinant in enterobacteria (see Section 3). The molecular weight of these plasmids is between 15×10^6 and 18×10^6 D[47]. In addition to the resistance to penicillin, they frequently also confer resistance to erythromycin and to heavy metal ions such as Cd^{2+}, As^{3+}, and Hg^{2+}[48].

The resistance to penicillin is due to the formation of penicillinases, *i.e.* enzymes that are inducible by penicillin[49]. Penicillinase plasmids can be divided into two groups on the basis of their mutual compatibility in a bacterial cell (see Section 8). These plasmids can not only exist in the extrachromosomal, autonomous state but can occasionally also be integrated into the host chromosome or into another plasmid that is present in the host cell[50]. These plasmids are not themselves transferable like the R factors of enterobacteria, but are presumably transferred by bacteriophages from one bacterial cell to another. A transfer process of this type is known as transduction.

5. Colicinogenic Factors (Col) of *Escherichia coli*

A large number of naturally occurring strains of *E. coli* have extrachromosomal DNA elements, known as Col factors, that among other unknown gene products code for the formation of colicins. The colicins are antibiotically active proteins that occur extracellularly[51] and have interesting modes of action. Their action is confined to colicin-sensitive strains of *E. coli* and closely related Enterobacteri-

aceae, in which they are able to inhibit protein biosynthesis, RNA or DNA synthesis, or oxidative phosphorylation. A model has been proposed for the mode of action of the colicins that involves an indirect effect of the colicin on the biochemical target[52-54]. This model is based on the following experimental observations.

Colicin molecules are adsorbed on specific receptors on the cell surface. The curve for the destruction of sensitive bacteria by colicins follows one-hit kinetics, *i.e.* an adsorbed colicin molecule can bring about the lethal action with a certain probability. The action of the bound colicin molecules can be eliminated if the cells are treated with trypsin shortly after their adsorption.

It has been deduced from these experimental findings that all colicins remain on the outside of the cytoplasmic membrane and influence the biochemical targets indirectly. All the biochemical changes observed in sensitive cells after the adsorption of colicins are concerned with the biosynthesis of macromolecules such as DNA, RNA, and proteins or the oxidative phosphorylation. All these processes are associated with the cell membrane in some way. It has therefore been deduced that the adsorption of a colicin molecule on the membrane initially causes a change in the receptor site, which in turn initiates the transmission of a signal to the target (protein biosynthesis, nucleic acid synthesis, oxidative phosphorylation). The mechanism of this indirect transmission is unknown. According to this view, the colicin does not pass inside the cell.

However, recent investigations on the mode of action of colicin E_3, which blocks protein biosynthesis, also points to a direct action of the colicin on the biochemical target. Thus colicin E_3 can fragment 16S r-RNA *in vitro*[55,56].

Some of the colicinogenic DNA factors, like the F factor and the R factors, possess transfer properties[57,58]. A few of these factors lead to pili similar to those produced by the F factor. The colcinogenic factor I (Col I), on the other hand, is an entirely different transfer factor. Though it causes the production of pili (I pili), these differ from F pili morphologically, in their antigenic properties, and in their adsorption capacity for specific bacteriophages[59,60]

6. Other Extrachromosomal DNA Factors with Transfer Properties

In addition to the three large classes of extensively studied extrachromosomal DNA elements [F (F'), R, and Col factors] there are a number of other extrachromosomal factors with transfer properties.

6.1. Hemolytic Factors (Hly) of *E. coli*

A number of pathogenic strains of *E. coli* are characterized by their ability to produce hemolysins. (Hemolysins are proteins that can lyse erythrocytes, see Fig. 7.) There appears to be a direct relation between the ability of these strains to form hemolysins and their pathogenicity[61]. *H. W. Smith* was the first to observe that the ability to form hemolysins is transferable at least in some hemolytic strains of *E. coli*, and is therefore presumably also determined by extrachromosomal DNA[62]. We were recently able to isolate two extrachromosomal DNA elements (Hly factors), which can occur either separately or together, from hemolytic *E. coli* bacteria[63,64]. Their molecular weights are different ($40—45 \times 10^6$ nd $60—65 \times 10^6$ D); they both carry the determinant for hemolysin production. The larger hemolytic DNA has derepressed transfer properties, whereas the transfer of the smaller hemolytic DNA is mostly repressed.

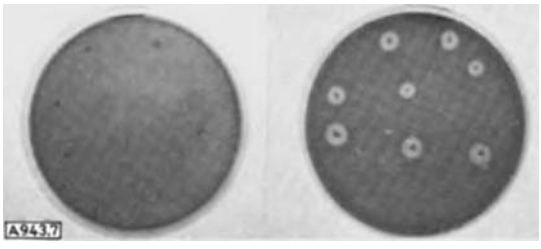

Fig. 7. Blood agar plate with hemolytic and non-hemolytic colonies of *Escherichia coli*. Left: non-hemolytic wild strain, right: hemolytic wild strain.

In the presence of the smaller DNA, the transfer properties of the larger are also inhibited. The smaller DNA presumably codes for a cytoplasmic transfer repressor that can also act on the larger DNA. The two hemolytic DNA factors exhibit extensive homologies in their nucleotide sequence, as has been shown by hybridization experiments. It may therefore be assumed that the smaller DNA was formed by removal of a number of DNA sections from the larger DNA, or that the larger DNA originated from the smaller factor by integration of additional DNA.

6.2. Other Factors

Other genotypic characteristics that are presumably transmitted by transferable plasmids are the ability to form enterotoxins[65] and to produce K-88 antigen[66] in *E. coli*. The production of H_2S in *E. coli*[67] and the degradation of D-camphor and octane by species of *Pseudomonas*[68] also appear to be determined by extrachromosomal transferable DNA elements. It is interesting to note that in the bacterium *Rhizobium trifolii*, which produces plant tumors, the genetic elements that determine the effectiveness (Eff^+) and the infectivity (Inf^+) also appear to be extrachromosomal in nature[69].

7. Plasmids with Unknown Properties

From the many plasmids to which it has not yet been possible to assign biochemical properties, let us consider here only one interesting group, *i.e.* the minicircular plasmids. These DNA molecules are characterized by the fact that they are unusually small. Their molecular weights range from about 1×10^6 to 3×10^6D. Any genetic information contained in these DNA molecules would thus be limited to one to six genes. The first plasmid of this group was isolated by *Cozzarelli et al.* from *E. coli* 15[70]. Other plasmids of similar sizes were isolated from wild strains of *E. coli* and characterized[71] (Fig. 8). It is interesting

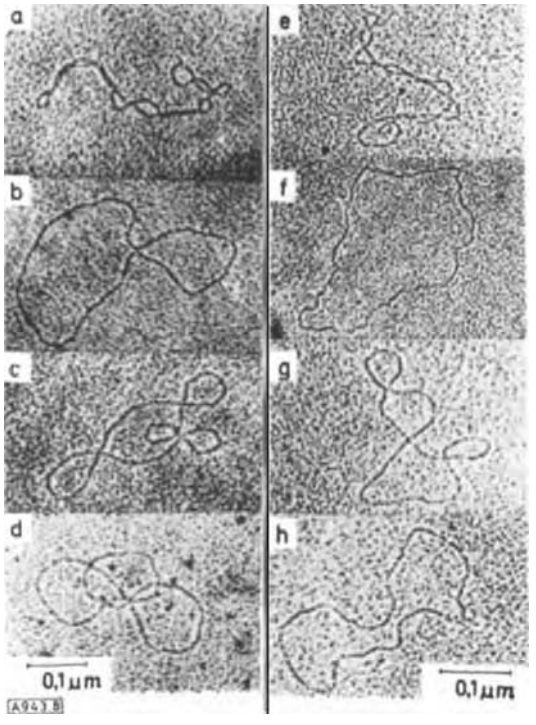

Fig. 8. Minicircular DNA, isolated from two wild strains of *E. coli*. a—d: Supercoiled (a) and open-ring (b—d) DNA from *E. coli* SC 78 (contour length 1.2±0.05 µm). e—h: Supercoiled (e) and open-circular (f—h) DNA from *E. coli* SC 79 (contour length 0.95±0.05 µm) (after [71]).

to note that these minicircular plasmids from *E. coli* exhibit extensive sequence homologies with one another and with the small colicinogenic factor E_1 (Col E_1) discussed earlier[71].

8. Compatibility between Bacterial Plasmids

A bacterial cell can simultaneously act as the host for several different extrachromosomal DNA factors if these plasmids are compatible with one another. It has been shown, however, that two very closely related DNA elements cannot exist stably together. Thus two related F factors, R factors, Col factors, or penicillinase plasmids cannot be stabilized at the same time in an *E. coli* cell, nor can an F factor in an Hfr cell.

On the basis of this phenomenon, the plasmids are divided into incompatibility groups. Members of such groups are incompatible with one another, whereas two plasmids from different groups can be present in the same host[72,73,45]. The incompatibility is thought to arise from the presence of specific plasmid attachment sites or replication sites, presumably on the membrane[74], which are essential for the stable incorporation of plasmids (see Section 11).

Temperature-sensitive mutants of *S. aureus* have been isolated that were no longer able to incorporate plasmids of one compatibility group stably at elevated temperature, though they could stabilize plasmids of another group, and *vice versa*[75]. It is thought that these mutants have no functioning membrane sites for the plasmids of the compatibility group in question at the restrictive temperature. It appears that only a limited number of such attachment or replication sites are available in the bacterial cell for a given group of plasmids. A plasmid entering a cell in which this site (or these sites) is (are) already occupied by another plasmid of the same compatibility group therefore cannot be replicated in this host and transmitted on cell division.

9. Physical Properties and Isolation Methods

The amount of extrachromosomal DNA in bacterial cells containing plasmids is generally approximately 0.5—3% of the chromosomal DNA. Most methods for the separation of extrachromosomal DNA from chromosomal DNA make use of the fact that all the bacterial plasmid DNA molecules found so far occur in a covalently closed, twisted (supercoiled) conformation. This compact conformation is converted into the more bulky open-circular conformation as a result of a break ("nick") in one of the two DNA strands, which may be brought about either mechanically (*e.g.* by shearing forces) or enzymatically by "nicking" endonucleases[76,77] (Fig. 9). In the supercoiled conformation the circular DNA molecule has physical properties that distinguish it from open-circular and linear DNA molecules:

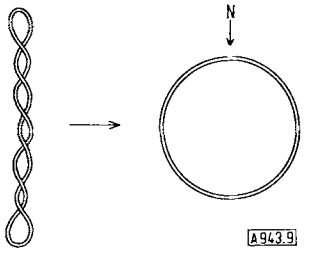

Fig. 9. Transition of a DNA from the supercoiled conformation to the open-circular conformation. The single-strand break or "nick" (N) is caused by endonucleases or by mechanical action.

It is less sensitive to shearing forces; the sedimentation rate in a neutral density gradient is higher[78]. The two strands of a supercoiled DNA molecule cannot be separated under denaturing conditions (pH = 11.5—12.5 or heating above the melting point), since they are joined topologically. Fast renaturation therefore occurs on neutralization to pH 7.0 to 8.0 or on cooling[79,80]. At pH 12.5 the denatured molecule, with its strands still joined topologically, assumes a very complex structure[80] whose sedimentation rate is approximately twice that in the supercoiled conformation in neutral solution[81]. Moreover, the buoyant density of the DNA in this compact conformation at pH 12.5 is 0.08 g/cm^3 higher than the buoyant density of the supercoiled conformation in neutral solution, whereas the buoyant density of the denatured strands of the open-circular form is only 0.06 g/cm^3 higher than that of the native form[82-84].

Supercoiled DNA binds intercalating dyes (*e.g.* ethidium bromide) more weakly than open-circular and linear DNA[85,86]. Since the binding of ethidium bromide to DNA is associated with a decrease in the buoyant density of the DNA, the relative decrease in the density of supercoiled DNA is smaller than that of a corresponding open-circular or linear form[85].

Most methods for the isolation of extrachromosomal DNA make use of the properties described. Only a brief description of the principles of the most important methods can be given below.

The first step in all isolation methods is lysis of the bacterial cells under mild conditions; shearing forces must be avoided and nucleolytic activities inhibited. The bacterial cells *(e.g. E. coli)* are therefore suspended in hypertonic buffer solutions and treated with lysozyme. This enzyme causes hydrolysis of the murein, an essential component of the cell wall of the bacteria. The resulting spheroplasts (bacterial cells that have lost an essential part of their cell walls) are lysed in the presence of sodium ethylenediaminetetraacetate (which inhibits the activity of deoxyribonucleases by complexing Mg^{2+}, Ca^{2+}, and Mn^{2+} ions) usually by detergents, but occasionally by osmotic shock or by treatment with alkali. The detergents that have proved most effective are sodium dodecyl sulfate, sarcosyl NL-30, sodium deoxycholate, and the nonionic detergents Brij 58 and Triton X 100. These last two are able to lyse spheroplasts of *E. coli* without destroying the complex of the cell membrane and the chromosomal DNA. This complex can therefore be removed by relatively low speed centrifugation (6000 × g), while the much smaller extrachromosomal DNA largely remains in the supernatant. The cell lysates obtained are subjected to the further purification steps either directly[87] or after removing the bulk of the chromosomal DNA as described[88].

The most important method for the purification of supercoiled DNA is probably equilibrium centrifugation in a cesium chloride gradient in the presence of an excess of ethidium bromide, which was first described by *Radloff et al.*[85]. In this process, the DNA is separated into a band of higher density, which contains the supercoiled DNA, and a band of lower density, which contains linear and/or open-circular DNA.

Another method makes use of the ease of renaturation of supercoiled DNA. Alkaline denaturation followed by neutralization, converts linear and open-circular DNA molecules into single-strand DNA, while the covalently closed DNA rings return to the supercoiled conformation. The supercoiled DNA can be separated by filtration through nitrocellulose, on which the denatured single-strand DNA is retained[89]. A corresponding separation can be achieved by chromatography on benzoylated or naphthoylated DEAE columns[90].

Because of its greater sensitivity to shearing forces (see above), linear chromosomal DNA can be fragmented more easily than the supercoiled extrachromosomal DNA by mechanical stirring. Subsequent sedimentation in an alkaline sucrose gradient (see below) results in the separation mainly of larger supercoiled DNA molecules such as F and F′ factors and R factors from the chromosomal DNA[91,92].

A method that was frequently used at first is based on the transfer of plasmids into host cells whose DNA has a different buoyant density *(e.g. Proteus mirabilis)*. The two DNA species can then be separated either by repeated equilibrium centrifugation in a CsCl gradient or by chromatography on columns packed with kieselgur coated with methylated albumin (MAK column)[93].

10. Special Plasmid DNA Molecules

The DNA purification methods described allowed the discovery of a series of interesting forms of plasmid DNA. Examples are the oligomeric and catenated DNA forms and the DNA replication intermediates[94–100].

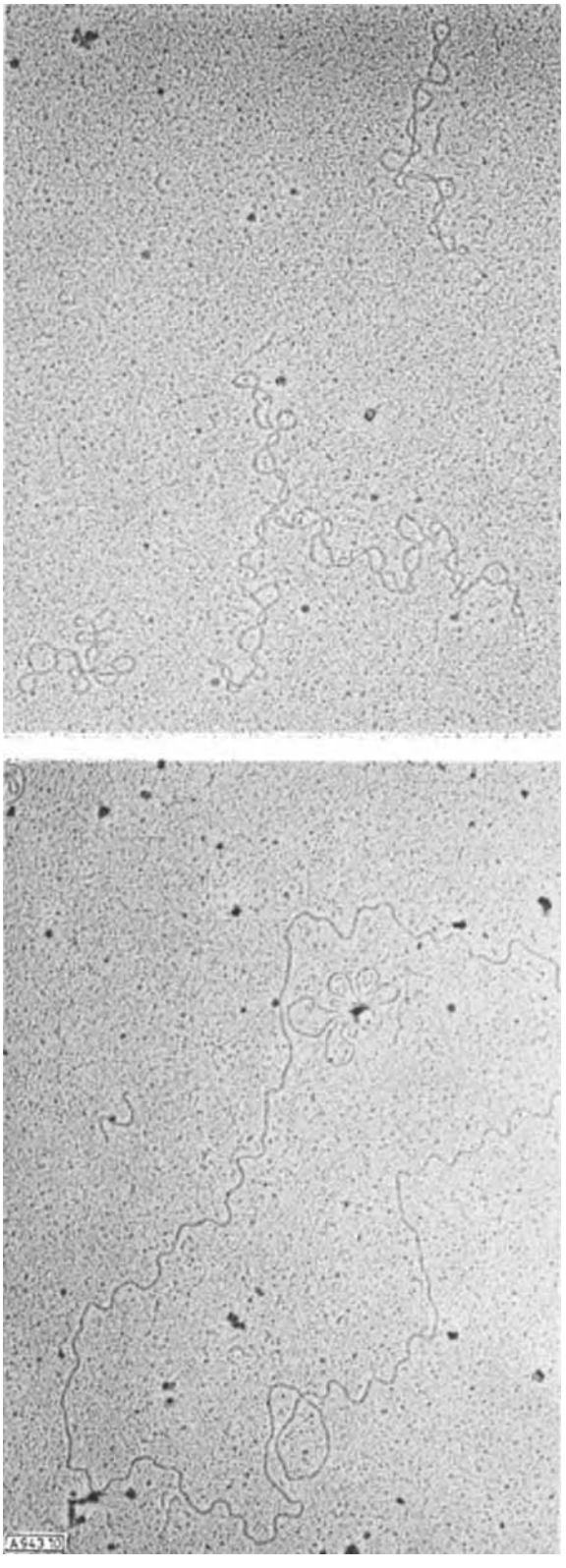

Fig. 10. Oligomeric DNA of the colicinogenic factor E_1 from *E. coli*. Top: two supercoiled monomeric Col E_1 DNA molecules and a supercoiled trimeric form. Bottom: open-circular trimeric Col E_1 DNA molecule (after [99]).

The term "oligomeric DNA" is applied to cyclic DNA molecules consisting of two or more covalently bonded identical genomes (Fig. 10), while in catenated DNA molecules two or more genomes are held together by topological bonding (as in catena compounds[101]) (Fig. 11). Oligomeric DNA molecules, like monomeric DNA, can occur in the supercoiled conformation and in the open-circular conformation. Their physical properties (apart from their size) and hence the isolation methods are the same as for the monomeric form.

Catenated DNA molecules, on the other hand, can assume different conformations and hence different properties, which affect their isolation. Catenated molecules consisting of only two components already offer three possibilities.

1. Both molecules are in the supercoiled conformation (Fig. 11a). Such a DNA molecule has the same properties (sedimentation, denaturation, dye adsorption) as a supercoiled oligomeric DNA of the same size, and can be distinguished from the latter by electron microscopy.

2. Both molecules are in the open-circular form (Fig. 11b). Such molecules cannot be distinguished from corresponding open-circular oligomers by their physical properties. Once again, differentiation is readily possible only by electron microscopy.

3. One molecule is in the supercoiled conformation and the other in the open-circular conformation (Fig. 11c and 11d). These catenated DNA molecules differ characteristically in their physical properties from supercoiled and from open-circular DNA of the same size. Their capacity to bind certain dye molecules (ethidium bromide) is logically intermediate between that of open-circular DNA and that of supercoiled DNA. In a CsCl-ethidium bromide gradient (see Section 9), therefore, these DNA molecules are found in a middle band between the heavy band of the supercoiled DNA and the light band of the linear and open-circular DNA[94]. The sedimentation behavior of these catenated DNA molecules in neutral and in alkaline gradients also differs characteristically from that of supercoiled and of open-circular DNA[94]. Catenated DNA molecules having three or more topologically linked components, which may in turn be monomeric or oligomeric forms, have also been isolated. Only very low concentrations of oligomeric and catenated DNA molecules occur in most plasmids under normal bacterial growth conditions. Formation of these DNA forms can however be enhanced at least for some plasmids[95,98,99,102–104].

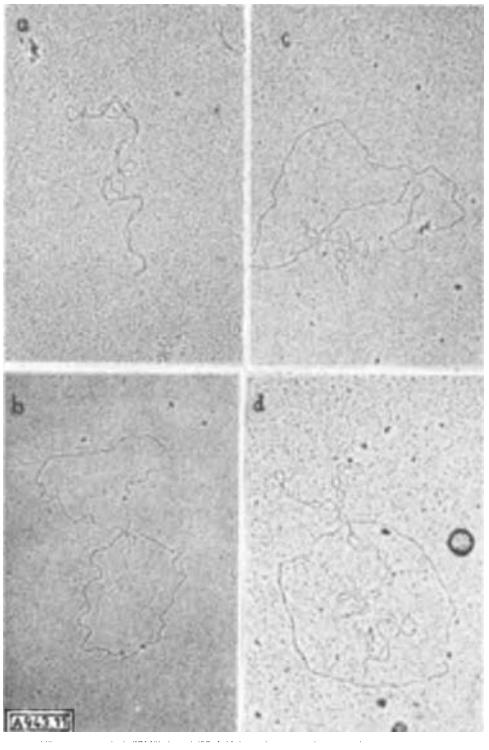

Fig. 11. Catenated DNA of the colicinogenic factor E_1 from *E. coli*. a) Catenate of two topologically linked supercoiled Col E_1 DNA molecules. b) Catenate of two open-circular monomeric Col E_1 DNA molecules. c) Catenate of a supercoiled monomeric and an open-circular dimeric Col E_1 DNA molecule. d) Catenate of a supercoiled trimeric and an open-circular dimeric Col E_1 DNA molecule (after [99]).

Two processes have been proposed for the formation of oligomeric and catenated DNA forms, *i.e.* 1) recombination[94], in which two plasmid DNA molecules are linked by breakage and reciprocal reunion (Fig. 12), and 2) erroneous replication[95] (Fig. 13) (see Section 11). The

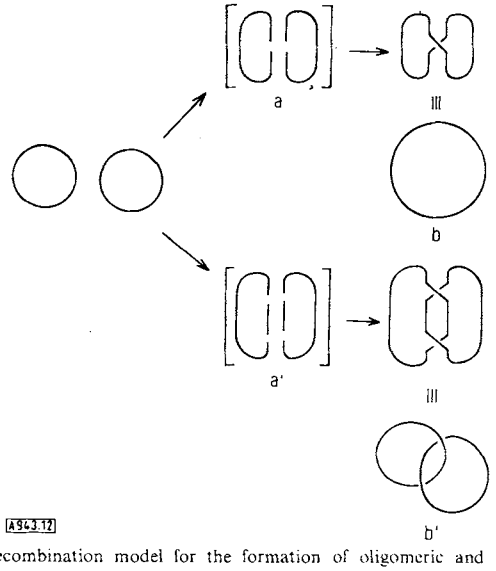

Fig. 12. Recombination model for the formation of oligomeric and catenated DNA molecules (modified model after [94]). The circular DNA molecules are broken either once (a) or twice (a'). With a single break, a reciprocal linkage gives a dimeric DNA molecule (b), whereas with a double break and reciprocal linkage, a catenated DNA molecule (b') is formed.

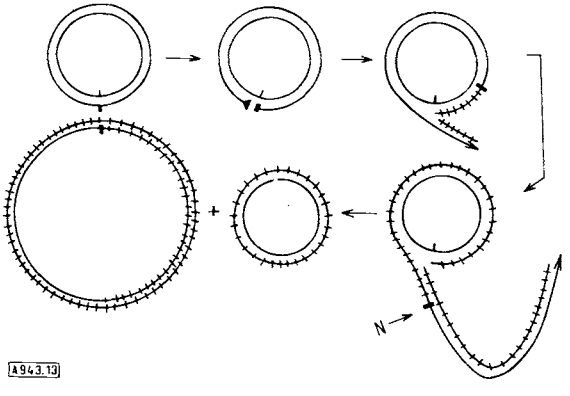

Fig. 13. Replication model for the formation of oligomeric DNA forms (modified model after [95], see also Fig. 16). The "error" in the replication here is that the endonuclease (N) cuts the linear strand, not after the first replication cycle, but only after the second (or third, *etc.*) cycle. Ring closure of the linear strand then leads to multiple (oligomeric) DNA molecules in addition to a monomeric DNA molecule. ——— parent (old) DNA, -HHHH- newly replicated DNA.

question which process is correct cannot yet be answered with certainty; a series of findings appear to support erroneous replication[95,105].

11. Replication of Extrachromosomal DNA Factors

There are a number of recent reviews[106–109] on the mechanism of DNA replication in bacteria, the details of which are still largely unknown. Only the broad features will be presented here, and known peculiarities of the replication of plasmid DNA will be pointed out. The replication of any autonomous genetic unit (replicon)[74] can be divided into three stages:

1. Attachment of the DNA to a specific replication site, which is presumably situated on the cell membrane of the bacterium[2].

2. Initiation of DNA synthesis[108], for which both a positive[74] and a negative[110] regulation mechanism have been postulated.

3. Elongation of the growing DNA chain by enzymatic polymerization of deoxyribonucleoside triphosphates, the two parent strands of the DNA acting as templates (Fig. 14)[111].

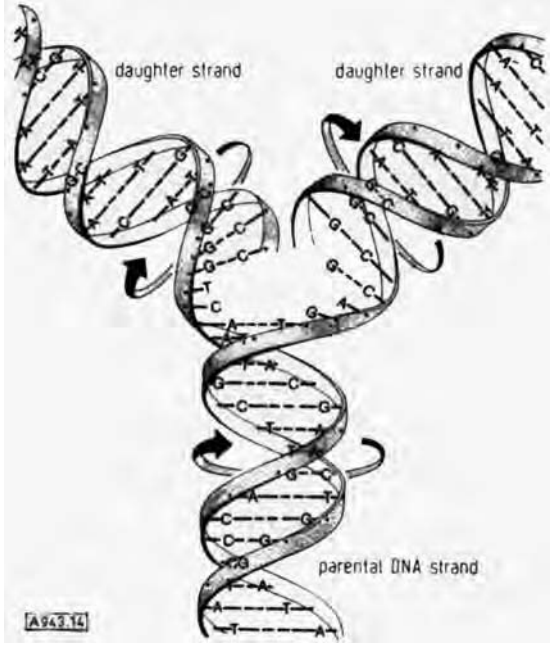

Fig. 14. Semiconservative replication of a linear DNA molecule.

Both for bacterial chromosomal DNA and for plasmid DNA, there is a body of evidence pointing to the existence of specific membrane attachment sites (see Section 8).

For the initiation of DNA synthesis of a covalently closed circular plasmid DNA molecule, a specific break in one of the two DNA strands, which allows the separation of the strands, has been postulated. It is not known whether this important step is regulated by a substance having a positive action (initiator) or by one with a negative action (repressor). The continuous synthesis of two proteins, which is influenced in different ways by chloramphenicol[106], is evidently a pre-requisite for the initiation of the synthesis of chromosomal DNA in *E. coli*. Chloramphenicol also inhibits the initiation of the DNA synthesis of many transfer factors. Interesting exceptions are the nontransmissible plasmids, the colicinogenic factor E_1 and the minicircular DNA of *E. coli* 15, both of which continue replication in the presence of chloramphenicol[71,113]. Other observations also indicate that more than one mechanism is involved in the initiation of plasmid DNA[98,114].

As has been shown by the isolation and the genetic characterization of temperature-sensitive DNA replication mutants, the elongation of chromosomal DNA in *E. coli* involves at least four proteins, though their biochemical nature is largely unknown[112]. These mutants exhibit normal synthesis of the chromosomal DNA at 30 °C, whereas the replication of this DNA stops at 40—43 °C. Biochemical studies on the replication of plasmids in replication mutants of this type in which the elongation is defective have shown that as in the initiation, there are also characteristic differences between the various plasmids in the elongation[98,122–124,127]. The difference in the dependence of the plasmid replication on the various DNA polymerases of *E. coli* is particularly interesting.

Since the isolation of a mutant (Pol A) that has practically no DNA polymerase I (Kornberg polymerase) activity, but nevertheless exhibits normal growth and normal synthesis of the chromosomal DNA[117], it has been assumed that the polymerase I plays no part in the semiconservative replication of the chromosomal DNA in *E. coli*, but is a repair enzyme for the DNA[118]. Two further DNA polymerases (II and III) have now been detected[119–121]. Recently *Gefter et al.* were able to show that a class of temperature-sensitive DNA replication mutants (dna-E mutants) have a temperature-sensitive DNA polymerase III activity[112]. This discovery shows that the polymerase III has an important function in the semiconservative DNA synthesis. This enzyme also appears to be responsible for the semiconservative replication of transfer factors. However, a number of experimental findings suggest that the polymerase I is involved in the replication of the colicinogenic factor E_1 and of the minicircular DNA of *E. coli* 15[122–124], whereas polymerase III does not appear to be necessary. DNA polymerase II does not take part in the replication of plasmid DNA in any of the systems investigated so far[121a].

Two models have been proposed for the semiconservative replication of circular plasmid DNA, *i.e.* the classical "Cairns model" (Fig. 15)[115] and the "rolling circle model" (Fig. 16)[116].

By electron-microscopy, both "Cairns structures" and "rolling circle" structures (circular DNA molecules with a double-stranded linear tail) have been found for Col E_1 DNA

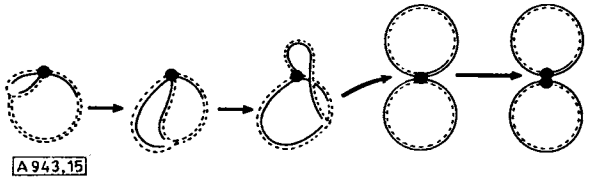

Fig. 15. Replication of a circular DNA molecule after *Cairns*. The model is based on the assumption that the replication always begins at the same origin and proceeds in the same direction (modified after [115]).

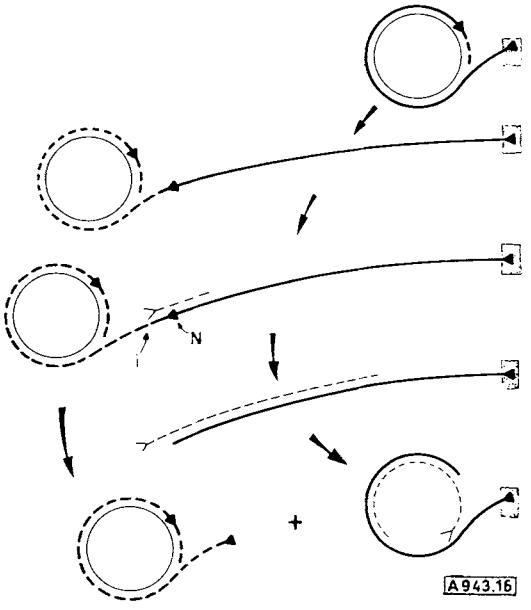

Fig. 16. Replication of a circular DNA molecule according to the "rolling circle model" of *Gilbert* and *Dressler*. One strand of the circular double-stranded DNA is opened and the free end is fixed to a membrane site. The broken strand is continuously withdrawn from the unrolling intact circular strand and replicated in steps (broken line). The initiation of the synthesis of the complementary strand begins on the withdrawn strand at i. An endonuclease (N="nickase") separates the replicating structure in such a way that two circular DNA molecules are formed after ring closure of the linear part (after [116]).

and for minicircular DNA from *E. coli* 15[97, 103, 104]. No definite conclusion can therefore be drawn as to which of the two models is correct for the replication of plasmid DNA. It is possible that both occur simultaneously.

Clear differences are found in the mode of replication of the various plasmids if one follows the behavior of the individual copies of plasmid DNA during a cell division cycle. If there is one copy of plasmid DNA per chromosome, the plasmid DNA is replicated synchronously with the chromosomal DNA, *i.e.* exactly one replication cycle of the plasmid DNA occurs during one replication of the chromosomal DNA. In the case of plasmids of which there are many copies per chromosome (*e.g.* Col E_1, minicircular DNA of *E. coli* 15, R factor NR 1 in *P. mirabilis*), though a constant number of DNA copies are replicated, the individual copies are randomly selected, *i.e.* during one replication cycle of the chromosome, some copies are replicated once, others twice or more frequently, and a corresponding number of copies not at all[125–127]. This random selection of the copies to be replicated suggests that either there are fewer specific replication sites on the cell membrane than there are DNA copies, or there are no specific sites at all in the cell for these plasmids (see Section 8).

The results described here indicate that the DNA replication of plasmids does not proceed by a single mechanism in which all the components are the same. This could also be evidence that more than one DNA replication mechanism is possible in the bacterial cell.

12. Closing Remarks

The bacteria, particularly the most extensively studied enterobacterium *Escherichia coli*, have an abundant supply of extrachromosomal DNA, which provides them with extra biochemical capabilities in addition to those determined by the chromosomal DNA. Though these additional genetic elements are described as "non-essential", they can offer the cell a decisive advantage in selection. It should also be recalled here that some plasmids, particularly the R factors, present a potential danger to man that should not be underestimated. Through their ability to inactivate antibiotics and to transfer this property to other suitable bacteria, and favored by the sometimes indiscriminate use of antibiotics, they lead to the development of increasing numbers of antibiotic-resistant strains among bacteria that are pathogenic to human beings, and these are then extremely unresponsive to therapeutic treatment with antibiotics. The specific properties of these plasmids, such as the ease of transfer from cell to cell and the ability to increase the information capacity by recombination make them variable genetic systems that are suitable for the rapid spread of genetic information.

Because of their small size, the plasmids are generally suitable subjects for investigations on fundamental questions connected with the establishment and self-duplication of genetic material in bacteria. The origin of these genetic elements is still completely unknown. In this connection, the reader can only be referred to speculations[12, 128]. The nature of most of the gene products that are determined by plasmids is also unknown.

The investigation of these DNA systems will undoubtedly enrich our understanding of the genetic and biochemical relationships in bacteria in the years to come.

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Structural Information from the Habit of Crystals

By Heinz Follner[*]

The question whether information about the internal structure of crystals can be deduced from their external form, *i.e.* from their habit, has often been discussed. A rule formulated by *Donnay* and *Harker* attempts to establish the relationship on the basis of structural geometry. Deviations from this rule make it clear that purely geometric correspondence criteria are only of limited application. Physical factors are also taken into account in the PBC vector method. A combination of the two methods can be of practical use in some cases for the determination of the crystal structures of organic compounds.

1. Introduction

The development of the determination of crystal structures has now reached such an advanced stage both theoretically and experimentally that it is possible to give details of the crystal structure and of bonds between the atoms. This should not lead us to forget that the processes responsible for the crystal structure are still largely unknown. Only in rare cases is it possible to explain satisfactorily why nature favors a certain crystal structure for a substance.

Since crystals first became the subject of scientific investigations, numerous studies have been concerned with the question of the relation between the external form of the crystal and its internal structure. A first step toward an understanding of crystalline substances was the discovery, in the 17th century, of the law of constant angles between corresponding faces of a given type of crystal. Identification of types of crystals was made possible by the mere discovery that every chemically uniform substance forms a characteristic group of crystal shapes. With the possibility of elucidating crystal structures by X-ray methods, the conditions were provided for the derivation of regular relationships between structure and morphological appearance.

1.1. Correspondence Between Structure and Crystal Form

The structure and the form of the crystal that grows are related by the equilibrium polyhedron. According to *Gibbs*[1], the specific free surface energy is of decisive importance to the habit of the crystals. The Gibbs-Curie law defines the surface polyhedron that exists when the free energy has reached a minimum. *Wulff*[2] was able to show that the converse of this law is also valid[3,4]. If the free surface energies of all the faces of a crystal are known, the equilibrium polyhedron can be constructed. Since the free surface energy (except in a few simple cases) cannot yet be given in a general form[5,6], this law cannot be applied to practical problems of crystal morphology. A further complication results from the fact that the equilibrium polyhedron and the actual growth form are rarely the same.

Another approach to finding a correlation between crystal structure and growth form is based on the strictly geometric structure of the crystal. As will be shown later, this approach falls short of requirements in many cases. The relationships indicated are shown in Figure 1.

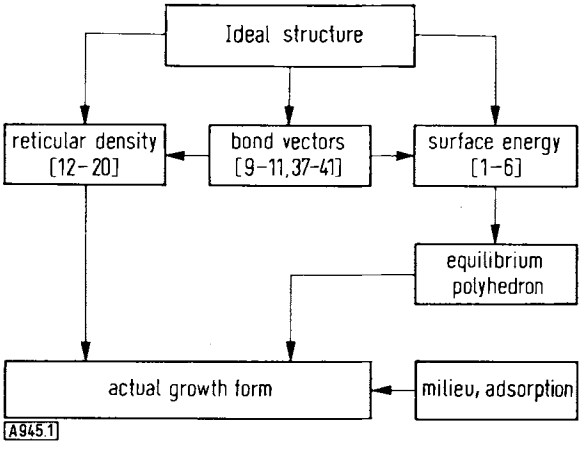

Fig. 1. Correspondence between crystal structure and morphological appearance [7].

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2. The Donnay-Harker Rule

2.1. The Bravais Law

Extensive morphological studies, particularly on the naturally occurring minerals, have shown that the number of different types of faces in a given type of crystal is small. The Miller indices (*hkl*) are generally simple whole numbers. This is easy to understand if one considers that the rate of growth of a crystal face is particularly dependent on irregularities such as steps or angles, which distinguish faces with higher indices. The great ease with which further structural components are deposited in these places is very impressively shown by the illustrations of decorated crystal faces containing structural faults such as screw or step dislocations (Fig. 2).

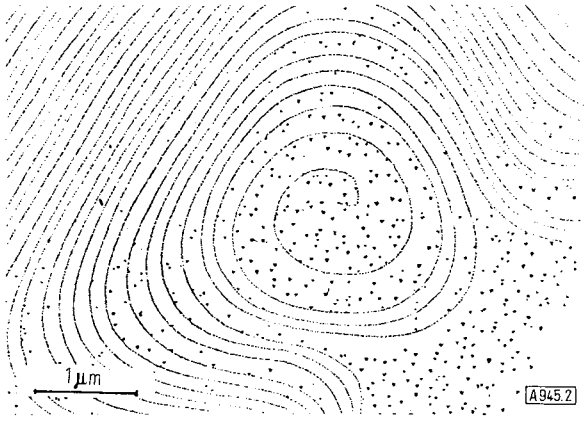

Fig. 2. Growth stages of a screw dislocation on a (111) face of a silver crystal [8].

Bravais[12] and *Friedel*[13–16] were able to correlate structure and external crystal form under the assumption that the crystal faces and the lattice planes are parallel. The morphological importance of a face increases with the density of its population of structural components. The reticular density of a lattice plane, which is defined as the number of atoms per (simple primitive) unit of area, is a measure of the morphological importance of a crystal face. The reticular density is thus proportional to the distance between lattice planes $d(hkl)$, whose calculation requires only the knowledge of the lattice constants. This simple criterion has proved effective for arranging faces in order of importance for a series of substances.

2.2. The Influence of Structural Symmetry on the Crystal Form

The 230 crystallographic space groups result from the combination of symmetry operations such as rotation, reflection, and translation. The combination of translation with rotation or with reflection leads to screw axes and glide planes respectively. These composite symmetry elements are contained in some of the 14 Bravais lattices, which, as basis, have the space groups as translation lattices. *Donnay* and *Harker*[17, 18] recognized that screw axes and glide planes change the population densities of lattice planes in certain zones, a fact that had already been pointed out by *Niggli*[19].

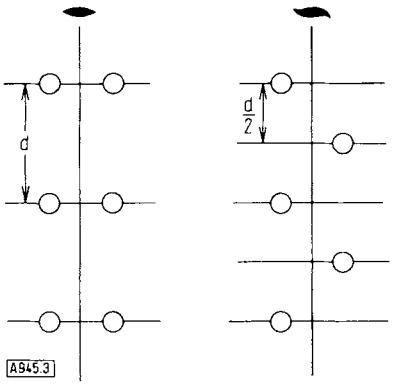

Fig. 3. Change in reticular density of lattice planes due to screw axes.

It is clear from the diagram of a twofold screw axis (Fig. 3) that, in contrast to a twofold rotation axis, intermediate layers with only half the reticular density arise normal to the axis. This fact reduces the morphological importance of this crystal face. A well-known example is quartz[18], which crystallizes in the trigonal space group $P\,3_1 2 (P\,3_2 2)$. Because of the threefold screw axis, the basal face (0001) is only eighth in the hierarchy of possible faces. Quartz crystals with developed (0001) faces are in fact rarely found (Fig. 4).

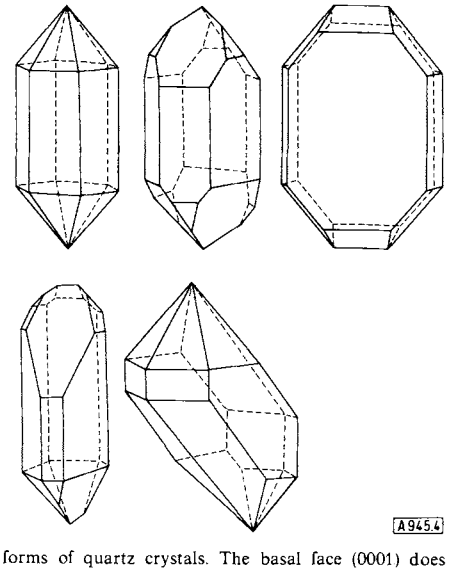

Fig. 4. Various forms of quartz crystals. The basal face (0001) does not occur here.

Glide planes have a similar effect on the reticular density of certain planes. Figure 5 shows a glide plane parallel to the plane of the drawing with a translation component along the *b* axis. The correct face hierarchy is obtained here by doubling the (0 *kl*) indices with *k* odd. It is significant that multiply primitive translation lattices (face-centered and body-centered lattices) also increase the reticular densi-

ties of certain lattice planes and so change the morphological hierarchy.

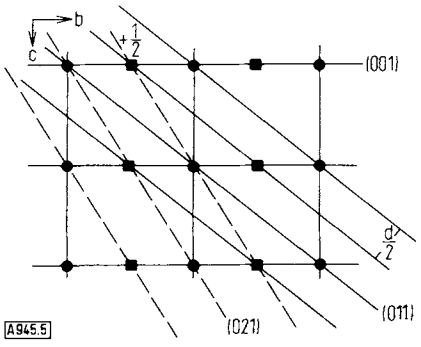

Fig. 5. Change in reticular density of lattice planes due to glide planes.

According to *Donnay* and *Harker* it is possible to set up a characteristic hierarchy of the face forms for each space group. This means that conclusions regarding the symmetry of the arrangement of atoms can be drawn from the crystal morphology. When this is carried out systematically for all 230 space groups one obtains 97 "morphological aspects", whose selection rules are closely related to the extinction rules of X-ray crystallography.

This method can be illustrated by two examples. The mineral garnet, $Al_2Ca_3(SiO_4)_3$, crystallizes in the cubic space group I a3d[18]. The dominant face forms are {011}, {112}, and {123}. Cubic and octahedral forms are rare. The occurrence of the first group of faces points to a body-centered unit cell. In a body-centered translation lattice, planes for which $h+k+l$ is even are favored.

X-ray structure determination has given the space group P mcn for aragonite[20, 21]. The face forms occurring in the three zones [100], [010], and [001] lead to the morphological aspect P *cn, which corresponds to the space groups P 2_1cn or P mcn. *Donnay* and *Harker*[17, 18] have successfully carried out investigations of this type on pyrite, sulfur, spinel, analcime, muscovite, goethite, lepidocrocite, columbite, baryte, and stephanite, among others. Further the method could be applied to phosphophyllite, hopeite, descloizite, strengite, variscite, and scorodite[22].

A method described by *Niggli*[23], in which crystal zones are emphasized as important structural directions, has a similar basis. Such directions are characterized by the shortest distance between identical structural components. The form system of a space group can be developed from specific zones.

2.3. Deviations from the Donnay-Harker Rule

The Donnay-Harker rule has given agreement of crystal and structural symmetries for many substances. As the volume of investigation results increased, however, cases of discrepancies between morphological and structural types became known. Deviations from a rule present grounds for a critical examination. The limits of applicability of the Donnay-Harker method will be discussed below.

1. The reticular density of the lattice planes by definition includes only coplanar structural components. The surface atoms are generally not on planes in the mathematical sense. The concept of the reticular density is therefore meaningful only if the thickness of the surface layer is negligible.

2. The general validity of the Donnay-Harker rule is also limited by the fact that the reticular population of the lattice planes, as a purely geometric factor, does not take the physical properties into account. A simple example of this is sodium chloride[18]. The dominant face form is the cube and not the octahedron. According to the Donnay-Harker rule, however, the (111) face should be favored in the space group F m3m. Cadmium oxide crystallizes in the same space group and in the same type of structure as sodium chloride. In this case, however, the preferred face form is {111}. The best agreement between the natural face hierarchy of sodium chloride and the hierarchy given by the Donnay-Harker rule is found if the structure is based on a simple primitive translation lattice. This is the case if no distinction is made between sodium and chlorine. The difference in behavior between NaCl and CdO is undoubtedly due to the difference in the type of bonding.

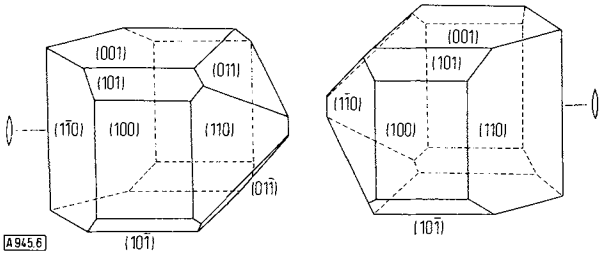

Fig. 6. Enantiomorphic crystal forms of tartaric acid.

3. The Donnay-Harker correspondence principle does not distinguish between parallel crystal faces of acentric space groups. The problem of the absolute configuration of a crystalline compound cannot be solved in this way. The attempt to determine the absolute configuration of tartaric acid from the morphological appearance[24] is therefore of interest in this connection. It can be seen from Figure 6, which shows two enantiomorphic crystals, that there are no parallel counterfaces to the sphenoid faces (011) and (01$\bar{1}$). *Waser*[24] thought that he could show in the structure found by *Beevers* and *Stern*[25, 26] (Fig. 7) that a difference exists according to whether a molecule is deposited on such a face from the left or from the right. *Waser* correlated this behavior with the absolute configuration of tartaric acid.

An X-ray study on a rubidium derivative[27] led to a different result, and showed that qualitative criteria are not generally sufficient to answer this question. It can also be quite problematic to decide whether such cases involve a structure-induced hemihedrism or whether environmental factors have influenced the crystal habit. The observation by *Turner* and *Lonsdale*[28] that the reason for the occurrence of the faces (011) and (01$\bar{1}$) without parallel counterfaces in the case of tartaric acid could be connected with

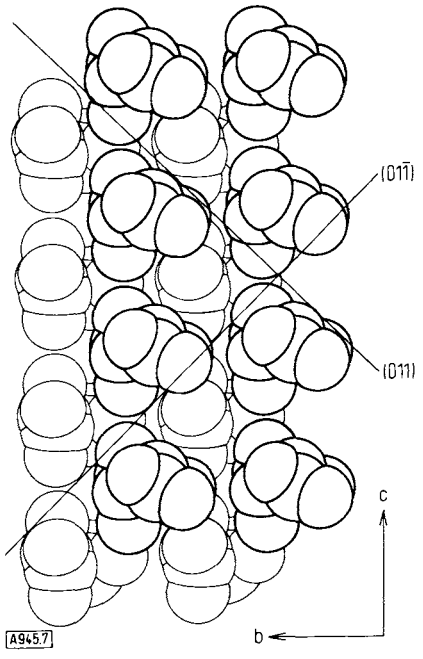

Fig. 7. Crystal structure of tartaric acid [24].

time-dependent hindrance by the solvent would only confirm the assumption that there are in fact differences in crystal growth along the polar axis.

4. The limit of applicability of the Donnay-Harker rule is also reached if the morphological symmetry of a crystal does not agree with the structural symmetry[29-31]. It is necessary to differentiate here between an increase (hypermorphism) and a decrease (hypomorphism) in the macrosymmetry in relation to the symmetry of the arrangement of the atoms. One case of hypomorphism is cuprite, Cu_2O, which was discussed in detail by *Kleber*[32], and which was long regarded as an example of the crystal class 432. According to its structure cuprite belongs to the crystal class m3m. Statistical studies give the face hierarchy {111}, {110}, {100}, {211}, {221}. According to the Donnay-Harker rule, however, {110} is the dominant face form. The preference for the octahedron is undoubtedly connected with the fact that the copper atoms in the structure form a face-centered lattice and the oxygen atoms form a body-centered lattice. Other examples of hypomorphism are α-sulfur (Fddd→222), phosgenite (P4/mbm→422), and sal ammoniac (Pm3m →422), while examples of hypermorphism are barytocalcite ($P2_1 \rightarrow 2/m$) and citric acid monohydrate ($P2_12_12_1 \rightarrow mmm$).

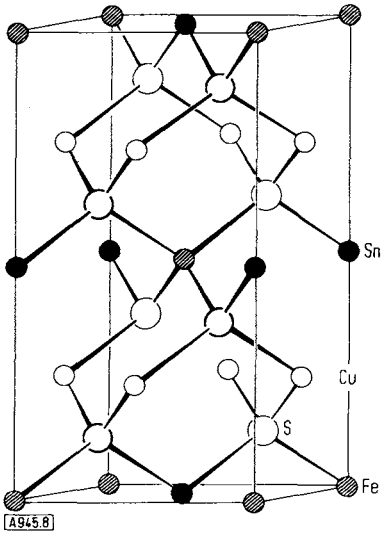

Fig. 8. Crystal structure of stannite, Cu_2FeSnS_4 [34].

An article by *Garrido*[33] on stannite, chalcopyrite, wulfenite, and manganite shows that in certain circumstances a differentiation between the structural symmetry and pseudosymmetry is possible on the basis of the statistical face frequency. For example stannite, Cu_2FeSnS_4, crystallizes in the space group $I\bar{4}2m$[34]. If no distinction is made between copper, iron, and tin atoms, the structure is based on a translation lattice face-centered on all sides (Fig. 8). The lattice constant in the c direction is thus halved. This pseudosymmetry is also shown by optical crystallometry. When the pseudomorphological aspect is taken into account, however, the face hierarchy is not characteristic of an F-lattice (Fig. 9).

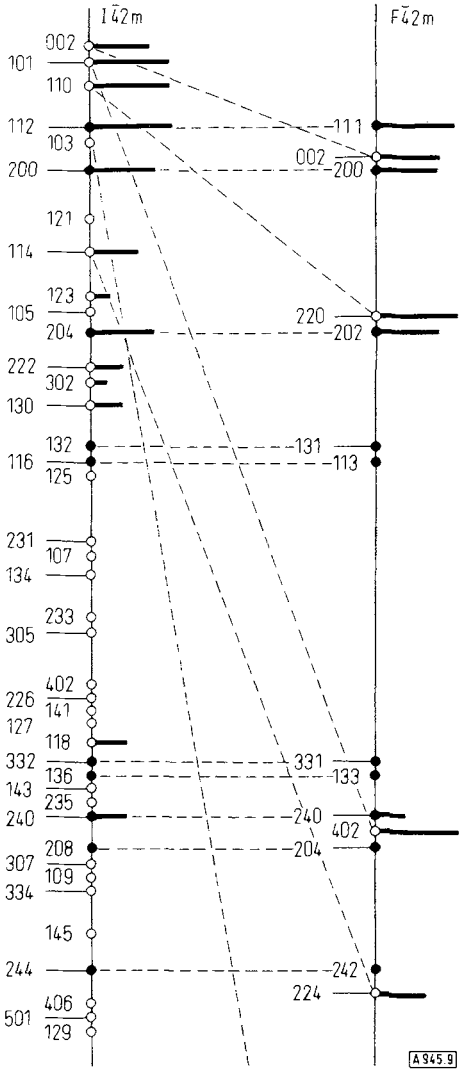

Fig. 9. Face hierarchy of stannite [33]. True symmetry: $I\bar{4}2m$; pseudosymmetry: $F\bar{4}2m$. The lengths of the horizontal full lines correspond to the statistical face frequency. Because of pseudomorphology the faces indicated by open circles change their position on the D-value scale.

In most types of crystals with discrepancies between structural symmetry and macrosymmetry, the structure determination has shown special arrangements of the atoms. The determination of the true structural symmetry can be made extremely difficult in these cases by the apparent presence of glide planes and screw axes. *Kleber*[35] has considered the structure of wulfenite ($PbMoO_4$) from this standpoint. Systematic absences of X-ray reflections lead here to the space group $I\,4_1/a$, which does not agree with the macrosymmetry (crystal class 4). *Kleber* found that certain displacements of the oxygen atoms do not cancel the extinction rule "$(hk0)$ only with $h(k)=2n$". The a glide plane is no longer a space-group-dependent symmetry element in this case. Accurate detection will not be easy if the shifts are only slight. *Leciejewicz*[36] unfortunately did not follow up *Kleber*'s suggestion in his redetermination of the structure of wulfenite.

3. The PBC Vector Method

The connection between structural and morphological elements certainly cannot be provided by criteria of the Donnay-Harker rule alone. It is clear from the departures from the rule that the external form of a crystal cannot always be explained by its structure. The concept of the reticular density of a lattice plane is a purely geometric quantity. It does not take into account physical factors such as bond character and electron density distribution.

An important advance in this respect was represented by the work of *Hartman* and *Perdok*[37-41], which provided the conditions required for the chemical bonding to be taken into account. The authors started from the assumption that the external form of the crystal is determined by bonds running through it like a chain. A strong bond vector has a decisive influence only if this bond continues uninterrupted through the entire structure. In complicated structures a chain of bonds may consist of several bond units. The effective direction is given by the vector sum of all the bond units. Since crystals have a three-dimensional periodic structure, one need only investigate the situation in the unit cell. The vector sum is known as the periodic bond chain vector (PBC vector). The rate of growth along such a direction is determined not by the strongest but by the weakest bond vector in the chain. *Hartman* and *Perdok* concluded that the position of a face in the hierarchy is determined by the number of PBC vectors running parallel to it. On this basis it was possible to group the crystal faces into three types:

1. F faces. These contain at least two PBC vectors.
2. S faces. Only one PBC vector runs parallel to these faces.
3. K faces. These contain no PBC vectors.

The three types of faces can be easily illustrated for the sodium chloride structure (Fig. 10). (010), (110), and (111) have the character of F, S, and K faces respectively. The situation is more complicated in the case of the barium sulfate structure. Investigation of the bonding showed that the principal crystal faces are F faces (Table 1). The occurrence of the single K face is attributed to the adsorption

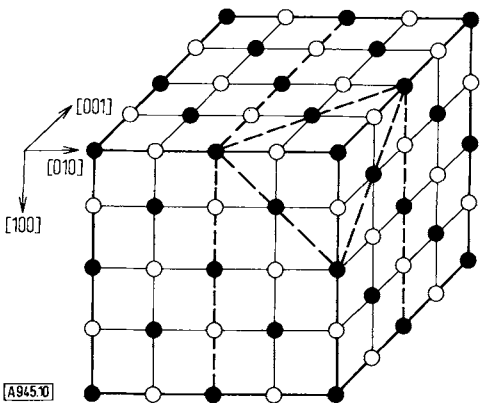

Fig. 10. PBC vectors in the structure of NaCl. The faces (010), (110), and (111) are indicated by broken lines.

of impurities. It is now known that the adsorption of foreign particles can alter the growth type of a crystal face.

Table 1. Face forms of barium sulfate [40].

Face symbol	Combination-persistence [%]	Face character (PBC)	(Donnay-Harker)
(001)	97.8	F	6
(210)	91.9	F	7
(101)	86.4	F	1
(011)	85.9	K	3
(010)	70.8	F	12
(211)	69.2	F	9
(100)	61.1	F	2
(410)	38.9	S	26
(102)	37.3	S	8
(111)	26.5	S	4
(213)	25.9	S	28
(230)	25.9	S	>29
(201)	24.4	S	5
(214)	16.7	S	>29
(212)	15.7	S	13
(310)	14.6	S	>29
(110)	11.4	S	16

This approach also explains why *Niggli*'s principle[23] of correspondence between lattice lines and zone axes cannot lead to agreement of a high order between morphological and structural elements. Lattice directions with the highest populations need not always correspond to the most stable zone axes.

4. Possible Applications

Concrete conclusions regarding structure can be drawn in certain cases by combination of the PBC vector method and the Donnay-Harker rule. *Hartman*[42] was able to determine the approximate positions of the centers of gravity of the molecules in the unit cell for a number of organic compounds (Table 2), knowing only the crystal form (cleavability) and the symmetry of the structure (space group, unit cell, cell content). The method is based on the following considerations. If a morphological face hierarchy $\{h_1k_1l_1\}$, $\{h_2k_2l_2\}^*$... *etc.* arranged according

Table 2. Coordinates of the centers of gravity of organic molecules calculated from morphological data. The comparison values in parentheses were taken from the known crystal structures [41].

Compound	x	y	z	Ref.
p-Chloroaniline	3/4 (0.7499)	1/4 (0.25)	0 (0.9932)	[43]
α-$(NSOCl)_3$	0 (−0.0747)	1/4 (0.25)	0 (−0.0647)	[46]
Papaine	1/4 (0.29)	1/8 (0.18)	1/4 (0.22)	[45]
Ribonuclease (orthorhombic)	0 (0)	0 (0)	1/4 (0.25)	[47]
Ribonuclease (monoclinic)	− (0.17)	0 (0)	3/4 (0.74)	[47]
α-Bromoisotutin	0 (0.0899)	2/3 (0.6715)	1/12 (0.0761)	[48]

to $d(hkl)$ values contains sets of indices whose faces do not appear on the crystal and that precede observed face forms in the hierarchy, the correct order can be found by multiplication of these indices by a whole number n: $\{h_2k_2l_2\}$*, $\{nh_1nk_1nl_1\}$, *etc.* The factor n will not generally be greater than two.

The knowledge of such additional "extinction rules" is necessary for the calculation of the coordinates of the centers of gravity. If $A(x_1y_1z_1)$ and $B(x_2y_2z_2)$ are the centers of gravity of two crystallographically identical molecules situated on parallel $(h_1k_1l_1)$ planes with an interplanar distance of $d(h_1k_1l_1)/n$, one obtains the simple relation

$$1/n = h_1(x_1 - x_2) + k_1(y_1 - y_2) + l_1(z_1 - z_2).$$

A number of compounds for which it has been possible to carry out these calculations are listed in Table 2. *p*-Chloroaniline[43] crystallizes in the space group P nma with four molecules in the unit cell. It follows immediately that the center of gravity of the molecule must lie on the reflection plane (at $y = 1/4$). The only face form found in the crystal is {111}. Arrangement according to $d(hkl)$ values gives the order {101}, {011}, {111}*, {002}, {200}, {102}, from which it follows that the indices of {101} and {011} must be doubled to obtain an order corresponding to the experimental findings. This fact can be used for the calculation of the center-of-gravity parameters with the aid of the above relation.

The coordinates of the centers of gravity can also be determined for papain[44] on the basis of similar considerations. Some interesting structural conclusions can be drawn even from Figure 11.

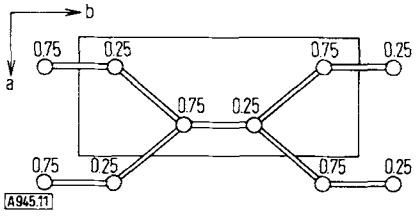

Fig. 11. Centers of gravity of molecules in the papain structure, projected on (001) [41].

Hazell[45] developed an "X-ray variant" as a supplement to this method. This author started with a structure consisting only of the centers of gravity of the molecules. The structure factor must give a maximum or a minimum for a face form that occurs on the crystal. If an unknown crystal face appears in the hierarchy before the face forms that occur, the structure factor in this case should be $F = 0$. As can be seen from Figure 12, the results of the calculations for α-$(NSOCl)_3$ agree with the values in Table 2.

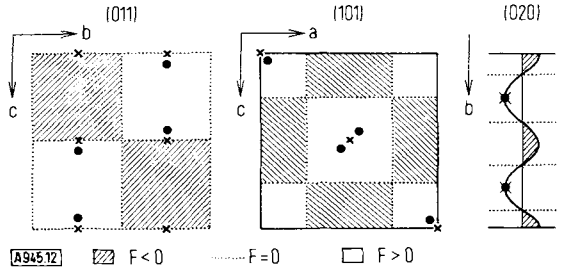

Fig. 12. Structure factor diagrams of the faces (011), (101), and (020) of α-$(NSOCl)_3$ [45]. Space group P nma, $Z = 4$; • : actual positions of centers of gravity; ×: possible positions.

5. Closing Remarks

The clarification of the correspondence between crystal form and internal structure is of great importance to crystal chemistry, and is undoubtedly helping toward a physical understanding of crystal structures. Though a large number of observations in this field have been reported in numerous publications, the Donnay-Harker rule is still the most effective method for the investigation of correspondence problems. However, this topic has been overshadowed somewhat in the past few years by the pure determination of structures. There is as yet no general basis for the clarification of the complicated processes that lead to the development of crystal faces. The discussion of the problems will certainly be more successful if more attention is given to the physicochemical processes instead of the purely geometric correspondence criteria.

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Very Low-Pressure Pyrolysis (VLPP); A Versatile Kinetic Tool

By D. M. Golden, G. N. Spokes, and S. W. Benson[*]

The theory and applications of the very low-pressure pyrolysis technique to the study of the rates and mechanisms of unimolecular reactions, radical-radical, and radical-molecule bimolecular reactions, surface recombination of atoms, heterogeneous reactions, and vibrational energy transfer are reviewed.

1. Introduction

It is the dream of every kineticist to have an apparatus which will give him a direct, unique, and quantitative view of all the products and reactants involved in an elementary chemical reaction. Various types of apparatus have been constructed to achieve this goal; some have come tantalizingly close to reaching the objective in special cases. But all too often, chemical complexity, secondary reactions, impurities, or surface reactions have turned the dream into a painful nightmare of incongruous or inconsistent results.

Perhaps the most ubiquitous difficulty dogging the experimental study of kinetic systems is that of secondary reactions. Frequently, the results of an initial chemical event in a simple system are completely concealed by a complex network of very rapid secondary processes. In the simple pyrolysis reactions of hydrocarbons, the olefin products generally start to change the course of the reaction after only 0.01 mol-% have been formed. It is equally difficult in oxidation studies to deduce initial steps from the multitude of complex products that are found in the very earliest stages of the reaction.

About eight years ago we constructed the "dream" system which appeared capable of giving direct, quantitative information on the rate of elementary, gas-phase chemical reactions. The principle behind the scheme was to flow a reactive gas at very low pressures into a heated Knudsen cell where it might decompose unimolecularly. Reactants and products would then flow molecularly (at large mean-free paths) through a relatively large exit hole into the ionization chamber of a mass spectrometer where they would be analyzed directly. At sufficiently low pressures, there would be no collisions between the products of the initial pyrolytic step and other species, and thus no secondary reactions. Because of this, we labeled the system "Very Low-Pressure Pyrolysis" or VLPP for short.

From its earliest days, VLPP has lived up to its expectations and proven itself capable of yielding information on the nature of the primary products of unimolecular, pyrolytic reactions. With the use of transition state treatments[1]

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of unimolecular reactions (both RRK and RRKM[*]), it has yielded Arrhenius parameters for unimolecular rate constants. In addition, it has been adapted quite generally to quantitative studies of fast bimolecular gas-phase reactions, as well as heterogeneous reactions. It also lends itself quite well to studies of energy transfer. Because of this general versatility of VLPP as a kinetic tool, we have felt it worthwhile to summarize our experiences with it and review some of its potential, as well as its demonstrated applications.

2. Some General Conditions for Operation of VLPP

If one wishes to eliminate secondary reactions in a chemical system, one thought suggests itself very quickly. Secondary reactions are generally bimolecular. Primary kinetic events are most often unimolecular. One can mitigate, drastically reduce, and even eliminate secondary, bimolecular reactions by working at sufficiently low pressures and for sufficiently short times.

Let R• be a radical or atom produced in a primary unimolecular event, such as bond fission, and t_r be the residence time of R• in the reaction system before it is observed or escapes. Let [M] be the concentration of any reactive species in this system (including, possibly, R•), and k_M be the bimolecular rate constant for attack of R• on M. Then the condition that very little secondary reaction occurs can be expressed:

$$f_r = t_r k_M[M] \ll 1 \qquad (2.1)$$

where f_r is the fraction of R• undergoing secondary reaction in time t_r.

If we arbitrarily select t_r as 10^{-3} seconds, and f_r as 0.01, then since $k_M \leq 10^8$ $lmol^{-1}s^{-1}$, for even very rapid radical-molecule reactions, the condition can be satisfied by choosing $[M] \leq 10^{-7}$ mol/l $\approx 4 \times 10^{-3}$ torr. Lower pressures permit us to increase t_r or k_M proportionately.

Such conditions require a flow system with very short residence times and very rapid quenching or sampling. The only analytical instrument that can accommodate itself to such small samples, and a wide variety of reactions is a mass spectrometer. One also requires relatively high temperatures to make initial rates fast enough. This, then, is the simple system illustrated schematically in Figure 1 for a VLPP experiment.

There is an immediate objection to such an experiment familiar to every kineticist. If the pressure is so low that there are no secondary reactions, then almost all collisions of both reactive molecules and products will be with the walls. Doesn't this experiment virtually assure that observed reactions will all be heterogeneous?

At first glance, such an objection seems very serious. However, heterogeneous reactions are usually slow reactions. They require a molecule or radical to reside on a surface or active site and then undergo chemical rearrangement.

[*] RRK and RRKM are abbreviations for the Rice-Ramsperger-Kassel and Rice-Ramsperger-Kassel-Marcus theories.

But the fastest competing reaction for such an adsorbed molecule is not chemical rearrangement with its relatively low A-factor and moderate activation energy, but rather reevaporation, which has a very high A-factor and usually a lower activation energy. Furthermore, as the temperature

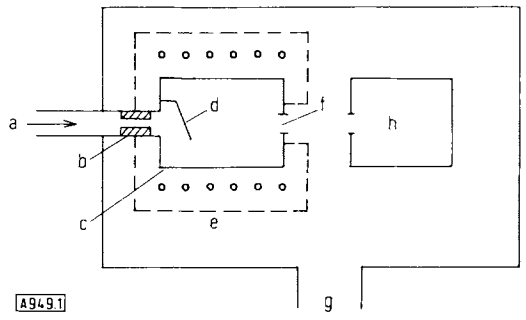

Fig. 1. Simple sketch of a VLPP apparatus. a = Gas inlet, b = capillary (i. d. 1—2 mm), c = Knudsen cell reactor, d = baffle to prevent molecular streaming, e = electric furnace, f = exit hole (2—10 mm), g = exit to very fast pumps, h = mass spectrometer detector.

increases, the residence time of a molecule or radical on the surface decreases. In fact, as we shall see in more detail later on, it is difficult to observe heterogeneous reactions in VLPP experiments. They need to have a collision efficiency with the surface usually in excess of 10^{-4} in order to be observed; thus, only very fast heterogeneous reactions can be measured with VLPP.

3. Scope of VLPP

In the eight years that have elapsed since our initial efforts at VLPP, the technique has become a refined and sophisticated tool for the quantitative study of very rapid reactions, both homogeneous and heterogeneous. We have operated VLPP from room temperature to 1400 °K with a quartz reactor and to 1900 °K with an alumina reactor. A brief summary of the range of problems to which VLPP has been applied is as follows:

a) To observe quantitatively the nature of the primary products of a unimolecular, thermal reaction, including both molecular or radical products.

b) Measurement of the rates of "fast" unimolecular reactions, *i.e.*, $10^{-1}\ s^{-1} \leq k \leq 10^4 s^{-1}$.

c) Measurements of the rates of "very fast" bimolecular reactions, *i.e.*, 10^{11} $lmol^{-1}\ s^{-1} \geq k \geq 10^{5.5}$ $lmol^{-1}\ s^{-1}$. These include atom-molecule, radical-molecule, and radical-radical reactions.

d) Measurements of the rates of "very fast" heterogeneous reactions, *i.e.*, collision yields $\geq 10^{-5}$. These studies have been done with atoms, molecules, and/or radicals.

e) Rates of energy transfer between highly excited molecules and surfaces or other molecules.

From a historical point of view, it is of interest to note that VLPP is the first technique to be generally applicable to the measurement of absolute rate constants for radical-

molecule reactions and radical-radical termination reactions.

4. Nature of the Experiment

In a simple VLPP experiment, molecules of reactant gas are allowed to flow under steady state conditions into a Knudsen cell reactor (Figure 1) made of fused silica (or other appropriate material) which is electrically heated in a controlled and uniform way. The flow rate is confined to a range such that the mean free path of molecules within the cell exceeds the exit aperture diameter by a factor of *ca.* ten. This guarantees molecular effusion in the exit beam. Usually the mean free path is kept longer than the vessel diameter so that most collisions of reactant molecules are with the walls. Under these conditions, "stirring" is very rapid and the reactor fulfills the kinetic requirements for behaving like a well-stirred reactor. That is, mixing of the entering gas with residual gas takes a time which is very small compared to t_r, the total residence time in the system[2]. Each Knudsen cell reactor of the type depicted in Figure 1 is characterized by a collision number,

$$Z_w = A_v/A_h \tag{4.1}$$

where A_v is the area of the walls of the reactor, and A_h is the area of the escape aperature. Z_w is the average number of collisions with the walls made by a molecule during its residence in the cell. The residence time, t_r, of the average molecule of mass M in the reactor is given by the Knudsen equation[3] as:

$$t_r = \frac{4V}{\bar{c}A_h}\ s^{-1} \tag{4.2}$$

where V is the volume of the reactor in cm^3, and $\bar{c}$ is the mean unimolecular speed given by kinetic theory as:

$$\bar{c} = \left(\frac{8RT}{\pi M}\right)^{1/2} = 1.46 \times 10^4 \left(\frac{T}{M}\right)^{1/2}\ cm/s \tag{4.3}$$

It is useful to define a first-order rate constant, k_{em}, which characterizes the rate of escape of a species of mass M from the reactor:

$$k_{em} \equiv \frac{1}{t_r} = 3.65 \times 10^3 \frac{A_h}{V}\left(\frac{T}{M}\right)^{1/2} \tag{4.4}$$

The frequency of collision of the average molecule with the reactor walls, ω, is given by:

$$\omega \equiv \frac{Z_w}{t_r} = Z_w k_{em} = \frac{\bar{c}A_v}{4V} \tag{4.5}$$

which depends *only* on the reactor geometry and not on its aperture size.

Reactor geometries and aperture sizes which we have employed have led to collision numbers ranging from *ca.* 100 to 20000 with collision frequencies of *ca.* $10^{4.5}\ s^{-1}$, implying average residence times from *ca.* $10^{-2.5}$ to 1 s.

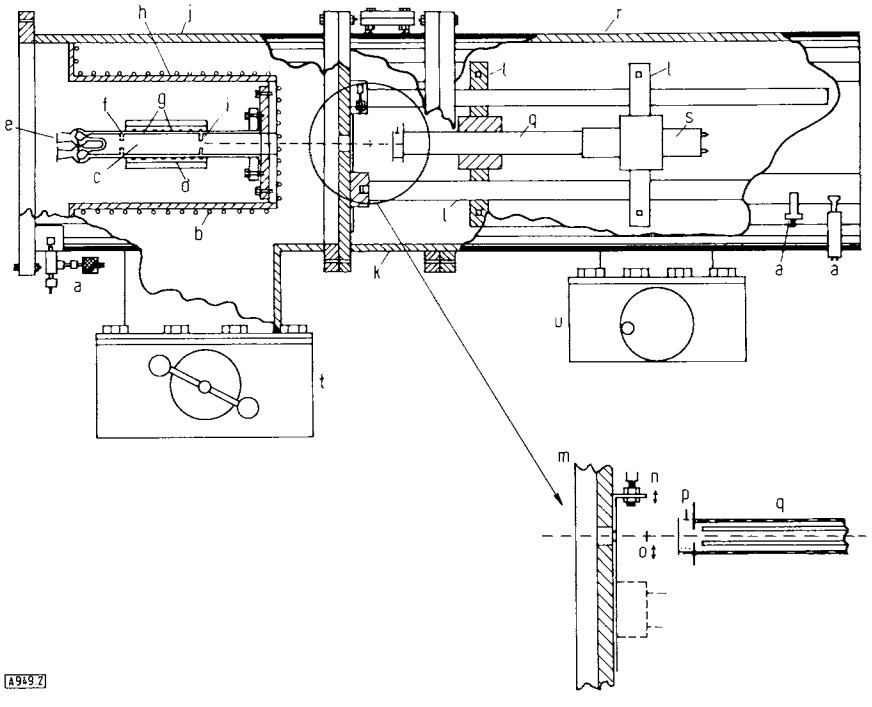

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Fig. 2. VLPP-II for studies of bimolecular reactions. Overall length of apparatus *ca.* 110 cm. a = Auxiliary inlet, b = water cooling, c = reactor, d = heater, e = gas inlet for reactants, f = baffles, g = thermocouple locations, h = reactor chamber, i = exit aperture, j = differential pumping chamber, k = central support section with electrical and mechanical access to system, l = spectrometer support, m = gas beam from reactor, n = adjustable collimater slit, o = vibrator (89 Hz), p = ionization chamber, q = quadrupole mass filter, r = mass spectrometer, s = multiplier (FW 141), t = six inch gate valve, u = four inch gate valve.

Gases which exit through the aperture are sampled with a quadrupole mass spectrometer, and the mass spectrum recorded.

Figure 2 shows a more complex arrangement which employs a differential pumping technique and allows higher flow rates to be attained in the reactor without unduly high pressures obtaining in the mass spectrometer (VLPP-II).

Figure 3 depicts a reactor which has been designed to allow the changing of aperture sizes *in situ*. This reactor, which we have called the "triple-aperture reactor" has been described in detail elsewhere[4].

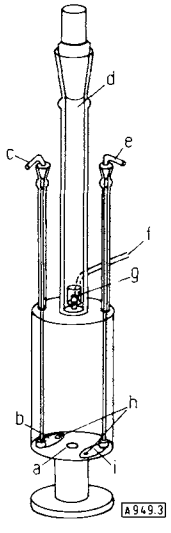


Fig. 3. Triple aperture quartz reactor system. a = Hole (1 cm dia.), b = aperture plate (3.3 mm dia.), c = 3.3 mm aperture plate manipulator, d = removable section with ground joint, e = 1 mm aperture plate manipulator, f = gas inlet tube, g = device for heating of solids and pyrolysis of emerging gases, h = aperture plates may be independently moved to cover 1 cm hole, i = aperture plate (1 mm dia).

If F_M is the flux of molecules M into the reactor cell, then under steady state conditions, with no reaction going on, the steady state concentration of M in the reactor is given by:

$$[M]_{ss} = \frac{F_M}{V k_{em}} = \frac{R_M}{k_{em}} \qquad (4.6)$$

V is the volume of the reactor and $R_M = F_M/V$ is the specific flux of M into the reactor. Typical fluxes have ranged from 10^{14} to 10^{17} molecules/s; typical reactor volumes are *ca.* 30—140 cm^3.

5. History of a Reacting Molecule

A molecule entering the Knudsen reactor through the entrance capillary (Fig. 1) is close to room temperature. It will make a few wall collisions in the entrance leads, and then it begins a sequence of collisions with the hot reactor walls. It probably reaches the translational and rotational temperature of the reactor walls within 3 to 5 wall collisions and then will probably take another 10 to 20 collisions to achieve something very close to the vibrational temperature of the reactor walls. Such a molecule is not, however, ready to react.

In order for a molecule to undergo unimolecular reaction, its internal (*i.e.*, vibrational) energy must exceed the activation energy of the particular reaction. Such highly excited molecules form an extremely small and exceptional population in the "tail" of the Maxwell-Boltzmann energy distribution. The unimolecular chemical reaction can be looked upon as an "indicator" which signals the appearance of such hot molecules in the energy spectrum.

There is consequently a natural "induction" period τ_i in VLPP experiments during which no chemical reaction takes place and which measures the time required for a population of cold molecules to achieve internal energies in excess of the activation energy for reaction.

If we select a temperature T at which the unimolecular reaction rate constant for a reactive molecule M exceeds 10^4 s^{-1}, and introduce M into a reactor cell of variable collision number Z_w, we may anticipate the behavior shown in Figure 4. At higher collision numbers the fraction of reacting molecules, x_r, slowly rises until it becomes proportional to Z_w, and then finally, with still greater Z_w, the fraction asymptotically approaches unity.

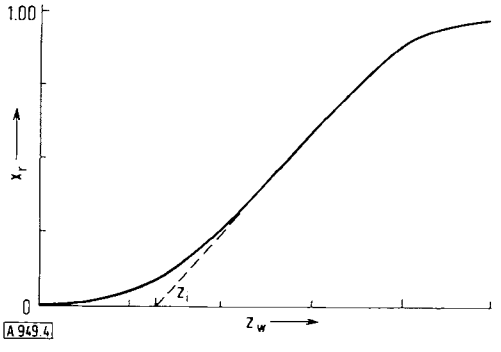


Fig 4. Fraction x_r of reacting molecules as function of the collision number Z_w.

If we extrapolate the linear portion of this curve to the axis, it will intersect at a value of $Z_w = Z_i$, which we can label the induction collision number. Z_i is essentially the number of collisions required for a molecule to reach an internal energy in excess of activation energy. It will turn out to be a measure of the rate of internal energy transfer ("chemical" accommodation) between a molecule and the walls of the vessel.

With most of the molecules we have studied, Z_i is less than 40 collisions, and we have so far been able to spend little time in this interesting area.

6. Unimolecular Decompositions

Let A be a molecule which can undergo an *irreversible* unimolecular decomposition whose stoichiometry is:

$$A \rightarrow pP + qQ \qquad (6.1)$$

If k_1 is the first-order rate constant for this process, and k_{ea} the first-order rate constant for A to escape from the vessel, then the steady state concentration of A is (eq. 4.6):

$$[A]_{ss} = \frac{R_A}{k_1 + k_{ea}} \tag{6.2}$$

and for a typical stable product, P, the steady state concentration is:

$$[P]_{ss} = \frac{p k_1 [A]_{ss}}{k_{eP}} \tag{6.3}$$

$$\text{Defining: } [A]_0 \equiv \frac{R_A}{k_{ea}} = [A]_{ss} \text{ when } k_1 = 0 \tag{6.4}$$

$$f \equiv \frac{[A]_0 - [A]_{ss}}{[A]_0} = \text{fraction of A decomposed} \tag{6.5}$$

$$F \equiv \frac{f}{1-f} = \frac{[A]_0 - [A]_{ss}}{[A]_{ss}} = \frac{k_1}{k_{ea}} \tag{6.6}$$

The essence of the technique can be ascertained from the understanding that equation (6.2) describes $[A]_{ss}$ as resulting from the competition between chemical reaction (k_1) and escape from the reactor (k_{ea}). VLPP is thus a relative rate measurement technique, wherein one of the processes is not a chemical reaction, but rather a physical process whose rate constant can be computed from easily known parameters of the experiment thus yielding *absolute* values of chemical rate constants.

The signal measured at the mass spectrometer detector can be calibrated as a function of the flow rate R_M for each reactant and product species M, and at constant temperature should just be proportional to the flux of M reaching the detector. If this signal is I_M, then:

$$I_M = \alpha_M k_{em} [M]_{ss} \tag{6.7}$$

where α_M is the calibration factor for species M.

For the unimolecular reaction (6.1) we can measure a signal I_A due to A or I_P due to any of the products P. Most of the time we have performed both reactant and product measurements. Mass balances are usually good to within about 5%. If we choose to follow reactant A, then:

$$I_A = \alpha_A k_{ea} [A]_{ss} \tag{6.8}$$

and

$$I_A^0 = \alpha_A k_{ea} [A]_0 = \alpha_A R_A \tag{6.9}$$

and from eq. (6.6):

$$F = \frac{[A]_0 - [A]_{ss}}{[A]_{ss}} = \frac{I_A^0 - I_A}{I_A} = \frac{k_1}{k_{ea}} \tag{6.10}$$

F is an experimentally measured quantity, as is k_{ea}. The constant k_1 is then calculated from eq. 6.10. The precision of measurement is greatest for $F = 1$ and least (unless measuring product) near $F = 0$ or very large. We usually confine our measurements to $1/9 \leqslant F \leqslant 9$ (*i.e.*, $0.1 \leqslant f \leqslant 0.9$).

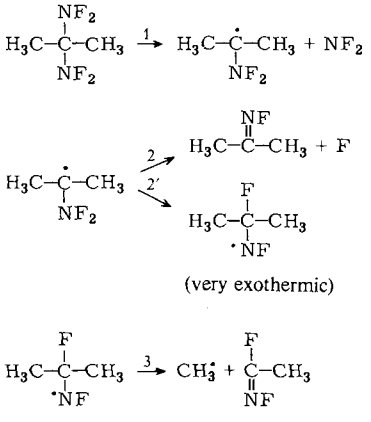
7. Some Unimolecular Product Studies

Our first studies of unimolecular reactions yielded very unexpected but interesting results. In the hope of detecting free radicals directly, as others had done with similar apparatus[5], we chose to look at the pyrolysis of 2-nitropropane. We anticipated finding NO_2 and isopropyl radicals. We did find[6], as we raised the reactor temperature, the expected disappearance of parent peaks, but no peaks corresponding to NO_2 or isopropyl radicals. Instead, we could identify what seemed to be a C_3H_6 mass spectrum and an unexpected spectrum of what could only be HNO_2. All search for radical fragments proved negative! Looking into the literature on NO_2 pyrolysis, we found that we had resolved an old controversy over its mechanism. Instead of radicals, the initial thermal step gives molecules in a direct, concerted process:

$$i\text{-}C_3H_7NO_2 \rightarrow HNO_2 + CH_2{=}CH{-}CH_3 \tag{7.1}$$

The mass spectrum of HNO_2 was confirmed by introducing an authentic sample into the mass spectrometer.

In a subsequent study of a class of related compounds, the substituted difluoramines, we verified that for both 1,1- and 1,2-bis(difluoroamino)propane, the initial thermal act was the fission of the relatively weak C—N bond to give free radicals and NF_2[7]. However, rapid secondary reactions occurred which were of great interest and which could be deduced from the residual spectra. One of these was an unexpected isomerization in competition with a secondary bond fission:



(7.2)

The fluoroimino products were identified from unique mass peaks which could not be accounted for in any other way and were subsequently confirmed by long-duration experiments in which the reaction products were trapped directly in a liquid nitrogen trap, isolated[8], and identified.

It was of particular interest to show, and we did, that there was no molecular elimination of HF from the 1,2-isomer or of HNF_2 from either species.

It was also of interest to observe that in the pyrolysis of 2-nitropropane, an unstable intermediate, HNO_2, was produced which did not decompose, while with the NF_2 compounds, radical intermediates were formed which did decompose. As we shall see, this is a typical feature of high-temperature, VLPP experiments, and one readily deduced from the theory of unimolecular reactions. HNO_2 has only a weak HO—NO bond (48 kcal/mol). It, nevertheless, doesn't decompose in our experiment with $t_r = 10^{-2}$ seconds, even at 1000 °K where its high-pressure unimolecular half-life would be about 10^{-5} second. The reason is that it is too small a molecule with too few internal degrees of freedom. In VLPP its rate has become second order and fallen off by a factor of more than 10^3. In contrast, the larger NF_2-containing radicals have many internal degrees of freedom and their rates are much faster in VLPP. In addition, they also have lower activation energies for fission or isomerization than HNO_2.

Similar studies[9] have revealed 1,2-elimination of H_2 from a saturated hydrocarbon. At about 1100 °K isobutane cleaves into H_2 + isobutene. The 1,2-elimination of H_2 from ethyl benzene has also been observed[10] as a much faster process than that for isobutane. These are theoretically interesting reactions, since they are "forbidden" by orbital symmetry rules, and we hope to be able to study them further.

Perhaps one of the most surprising of our primary product studies came in the observation of the pyrolysis of monomethyl hydrazine[11]. Instead of the expected split into amino and methylamino radicals, we were able to demonstrate that primary decomposition was wholly into stable molecules, $NH_3 + CH_2{=}NH$ and $H_2 + CH_3{-}N{=}NH$.

8. Relationship of k_1 to $k_{1\infty}$

The rate constants k_1 (and, of course, those for the reverse reactions) will be a function of ω, the frequency of collision of the average molecule with the walls of the reactor. This is a result of the fact that the frequency of wall collisions is not sufficient to maintain an equilibrium distribution of energy in the reacting molecules and thus the rate constant measured is lower than $k_{1\infty}$, the constant for $\omega \rightarrow \infty$. This is commonly referred to as "fall-off" since a plot of k_1 vs. ω shows the fall-off of k_1 from the value $k_{1\infty}$.

The relationship between k_1 and $k_{1\infty}$ is given by RRK(M) theory, and it is possible to predict k_1 if the Arrhenius parameters of $k_{1\infty}$ are known. Accordingly, if the value of the Arrhenius A-factor is known, the value of the activation energy may be determined from a fit of k_1 vs. T to a computed curve. Details of such determinations of activation energies are given in several publications[4].

In general, A-factors for unimolecular processes can be estimated with considerable accuracy if the process is unambiguous. If, on the other hand, doubt exists as to whether a given process is occurring *via* bond homolysis or molecular elimination, estimated A-factors may differ by *ca.* $10^{3\pm1}$ s^{-1}, and both would still give good fits to a k vs. T curve, albeit, of course, for different values of the activation energy. Often VLPP can answer questions of this type *via* the mass spectral product analysis, since few, if any, secondary reactions will have occurred.

9. Arrhenius Parameters for Unimolecular Rate Constants

One of the simplest examples of a reaction of this type is the dehydroiodination of isopropyl iodide. The high-pressure Arrhenius parameters are well known[12] and the determination of k_1 by VLPP can be thought of as a test of the method granting the correctness of the RRK(M) treatment. The results of pyrolyzing isopropyl iodide in the triple-aperture reactor (Fig. 3) using VLPP-I apparatus are compared with the RRKM *predicted* values in Figure 5(a)[4].

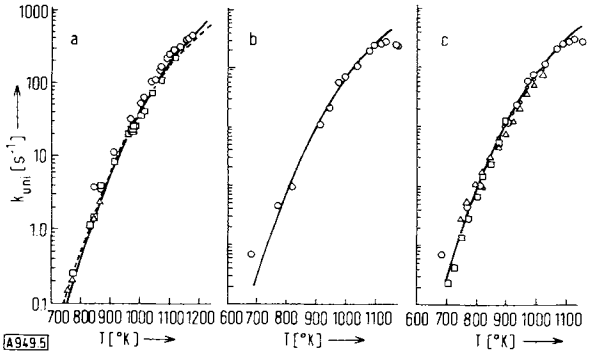


Fig. 5. Elimination of HI from isopropyl iodide; plot of k_{uni} as function of T. a) Measurements in apparatus VLPP-I. ——: RRK plot, – – –: RRKM plot. –○–○–: $Z = 285$, –□–□–: $Z = 1920$, –△–△–: $Z = 22400$. b) Measurements in apparatus VLPP-II. –○–○–: $Z = 2000$. c) Measurements in apparatus VLPP-III. –○–○–: $Z = 29000$, –□–□–: $Z = 1930$, –△–△–: $Z = 176$. All three cases gave the values $E_0 = 44.4$ kcal/mol, $\log A_\infty = 13.69\ s^{-1}$, $E_\infty = 45.5$ kcal/mol.

Isopropyl iodide has also been pyrolyzed using a VLPP-II apparatus (Fig. 2) in a *ca.* 2000-collision reactor with ω higher by 1.88 than in the triple-aperture reactor; the results are shown in Figure 5(b). A third VLPP apparatus (VLPP-III) modeled directly on VLPP-I, has been constructed at Stanford Reasearch Institute by Drs. *D. S. Ross* and *L. Piszkiewicz*. The results of isopropyl iodide pyrolysis in their "triple-collision" reactor are shown in Figure 5(c).

The agreement among the results from the three different VLPP systems is taken to indicate, with a great deal of certainty, the efficacy of the technique.

n-Propyl iodide pyrolysis has also been investigated[4]. We wanted to obtain a value for the activation energy of the dehydroiodination of *n*-propyl iodide as a quantitative measure of the difference between the value for this anti-Markownikoff process and the Markownikoff elimination in isopropyl iodide. VLPP seemed well adapted to this study as static systems are complicated by the presence of the I atom catalyzed HI elimination.

The VLPP of *n*-propyl iodide did indeed produce propylene and HI, but in competition with the production of *n*-propyl radicals and I atoms. The radicals quickly split to give ethylene and CH_3, so that by monitoring total iodide

disappearance, and both ethylene and propylene appearance, both rate constants could be measured.

RRK theory was properly modified to take into account the competition between the processes and the results are shown in Figures 6 and 7.

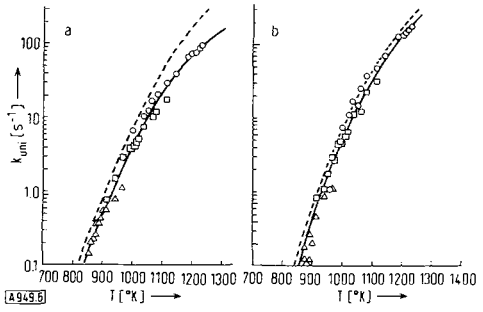


Fig. 6. a) Elimination of HI from *n*-propyl iodide; plot of k_{uni} as a function of *T*. ——·——: RRK/2 plot; – – –: RRK plot; - o - o -: $Z = 285$, – □ – □ –: $Z = 1920$, – △ – △ –: $Z = 22400$; $E_0 = 47.5$ kcal/mol, log $A_\infty = 12.9$ s^{-1}, $E_\infty = 48.4$ kcal/mol. b) Cleavage of C—I bond in *n*-propyl iodide; k_{uni} as a function of *T*. Key to curves as in Fig. 6a. $E_0 = 52.0$ kcal/mol, log $A_\infty = 15.5$ s^{-1}, $E_\infty = 54.9$ kcal/mol.

A number of other reactions have been investigated purely as a demonstration of the efficacy of the method. These include the pyrolyses of ethyl acetate[13], cyclobutane[14], and di-*tert*-butyl peroxide[15]. Only cyclobutane yielded other than a simple verification that VLPP results agreed with the high-pressure parameters. The agreement between the VLPP results and the previously determined values of the Arrhenius parameters in all but the cyclobutane pyrolysis, lend credence to the suggested changes in the cyclobutane values[14].

2,3-Dimethylbutane and 2,2,3,3-tetramethylbutane[16] have been pyrolyzed and found to fit the rate parameters measured by *Tsang*[17, 18].

In the course of using them as thermal sources of methyl, ethyl, isopropyl, and *tert*-butyl radicals, we have pyrolyzed di-*tert*-butyl peroxide, di-*tert*-amyl peroxide[15], azoethane, dipropionyl peroxide, azoisopropane, and 2,2'-azoisobutane[19].

In the case of di-*tert*-amyl peroxide, if the *A*-factor is assigned in a manner analogous to di-*tert*-butyl peroxide, where the high-pressure parameters are already known, the value of the activation energy which matches the observed data best is within 1 kcal/mol of the value for di-*tert*-butyl peroxide. *Tsang*[20] observed the same sort of lowering for *tert*-amyl vs. *tert*-butyl bond dissociation energies.

The results for 2,2'-azoisobutane can be compared with previous high-pressure results in both static[21] and flow[22] systems. (The value preferred in Ref. [12] is not correct.)

In earlier work[23] *Benson* and *Spokes* showed that the elimination of HCl from 1,1,1-trichlorethane was compatible with the parameters already established[24] in high-pressure work.

In an unpublished qualitative preliminary study[25] *Spokes* and *Golden* have pyrolyzed C_2F_4 and found their results compatible with C—C bond scission at a rate compatible with the known thermochemistry of CF_2 radical production.

Other examples of reactions of this category that have been studied by VLPP include the pyrolyses of the three benzylamines, $PhCH_2NH_2$, $PhCH_2NH(CH_3)$, and $PhCH_2N(CH_3)_2$[26]. Here the reactions were benzyl-N bond homolyses, and a reasonable choice of *A*-factors led directly to values of the heats of formation of the aminyl radicals. (There are secondary reactions in these systems—namely, radical decompositions and, perhaps, disproportionations—but as long as there is no recombination to reform the reactant or reactions which destroy it, other than the unimolecular decomposition, equation 6.10 holds.)

Table 1 shows the results of investigations on several other nitroalkanes (using VLPP-III).

Table 1. Kinetic data for some nitroalkanes (VLPP-III)[a]

Cpd.	log *A* [s^{-1}]	E_a [kcal/mol]
$(CH_3)_2CHNO_2$	11.3	39 ± 1
$CH_3CH(NO_2)CH_2NO_2$	11.5	41 ± 1
$CH_3CH_2CH(NO_2)_2$	17.5	47 ± 1
$CH_3C(NO_2)_2CH_3$	17.5	46 ± 1
$CH_3CH_2CF(NO_2)_2$	17.5	47 ± 1

[a] These investigations were sponsored by the U.S. Office of Naval Research. The results are preliminary data presented prior to publication and were kindly supplied by Dr. *D. S. Ross* and Dr. *L. Piszkiewicz* of the Physical Organic Chemistry Department of the Stanford Research Institute.

All alkanes with geminal nitro groups undergo C—N scission at about the same rate. The C—N bond strength in each of the three molecules is 46 to 47 kcal/mol, *i.e.* the effects of H-, CH_3-, and F-substitution at C-1 on the C—N bond strength are apparently the same. The nongeminal 1,2-dinitropropane, on the other hand, has a C—N bond strength of *ca.* 60 kcal/mol, and undergoes faster cyclic elimination of HONO. Comparing 2-nitropropane with 1,2-dinitropropane shows that the second NO_2 in the dinitro compound seems to have little effect on the rate of elimination.

10. Radical-Molecule Reactions

Since it is possible to work up to pressures of 4×10^{-2} torr in vessels with 1 mm exit diameter holes, VLPP can be used to study fast bimolecular reactions. These include reactions which go at virtually every collision ($k_B \approx 10^{11}$ lmol^{-1} s^{-1}) to those which have a collision yield of one in 10^5 ($k_B \approx 10^6$ lmol^{-1} s^{-1}).

Between temperatures of 300 and 1500 °K, very few, if any, bimolecular reactions between stable molecules have rate constants of this order of magnitude. Only radical-molecule and radical-radical reactions are so fast. We have studied both in VLPP.

To study radical-molecule reactions in VLPP, we need a source of radicals and a method for introducing molecules at known concentrations. Conventional pyrolysis techniques can be used to provide radicals and we have, for example, produced CH_3 radicals by the pyrolysis of di-*tert*-butyl peroxide. At temperatures in excess of about 500 °K,

this molecule decomposes rapidly into 2-*tert*-butoxyl radicals, which in turn rapidly decompose into two CH_3 radicals + two acetone molecules. Above 700 °K in a 1000-collision reactor, one finds essentially quantitative decomposition into $2CH_3^{\cdot} + 2CH_3COCH_3$.

As radical sources we have also used: acyl peroxides $[(n\text{-}C_3H_7\text{—}CO_2)_2 \rightarrow 2C_3H_7^{\cdot} + 2CO_2]$, azo compounds $(R_2N_2 \rightarrow 2R^{\cdot} + N_2)$, oxalate esters $(ROCOCO_2R \rightarrow 2R^{\cdot} + 2CO_2)$, and peroxyesters $[(RCO_2OR') \rightarrow R^{\cdot} + R'O^{\cdot} + CO_2]$.

Chemical reactions can thus be used to produce free radicals and the second reactant can be introduced by premixing in known amounts with the reactive radical source or else through a second inlet. Each inlet system supplies reagent with or without added carrier gas[*] *via* a controllable flow system which can be quantitatively calibrated over a flow range of 10^{13} to 10^{17} molecules/s.

One of the first reactions studied was[27] that between CH_3 radicals and O_2. For over 40 years now, this reaction has been proposed as one of the key, fast steps in hydrocarbon oxidation with a stoichiometry:

$$CH_3^{\cdot} + O_2 \rightarrow CH_2O + {}^{\cdot}OH \qquad (10.1)$$

However, we were able to show that over the temperature range 500—1400 °K, there was no measurable CH_2O produced in over 10^4 collisions of CH_3 with O_2. Assuming an Arrhenius A-factor for such a reaction of 10^8 $l\,mol^{-1}\,s^{-1}$, this implies an activation energy E_1 in excess of 14 kcal. If the A-factor is $10^{9.5}$, as it is for the addition reaction, then $E_1 \geq 24$ kcal. These results essentially rule out reaction (10.1) as a significant contributor to hydrocarbon oxidation.

Similar studies[28] with allyl radical and O_2 show that it too does not react with O_2 in over 10^4 collisions; consequently, the proposed reaction

$$\dot{C}H_2\text{—}\dot{C}H\text{—}\dot{C}H_2 + O_2 \rightarrow CH_2{=}CH\text{—}CHO + HO^{\cdot} \qquad (10.2)$$

also has a high activation energy and is not an important reaction in the oxidation of C_3H_8 or of C_3H_6.

In contrast, the reaction $CH_3^{\cdot} + NO_2$ gave copious yields of CH_2O *via:*

$$CH_3^{\cdot} + NO_2 \rightarrow (CH_3ONO)^* \rightarrow CH_3O^* + NO \qquad (10.3)$$
$$\downarrow$$
$$CH_2O + H$$

While we made no effort to obtain quantitative data on the overall reaction, the rate constant must be in excess of $10^{9.5}$ $l\,mol^{-1}\,s^{-1}$ with $E_{act}=0$. Allyl radicals also react rapidly with NO_2.

Our first extensive measurements of radical-molecule reactions were made with the reaction of CH_3 radicals with DBr[29] using a dual entry reactor. If we use the reaction of $CH_3^{\cdot}$ (from pyrolysis of di-*tert*-butyl peroxide with HI, as an example of the method, we can titrate $CH_3^{\cdot}$ with HI by progressively increasing the concentration of HI (*i.e.*, flow of HI) in the reactor at fixed flow of peroxide. The CH_3 radicals formed in the pyrolysis have the possibilities of either escaping from the reaction vessel or of reacting with HI. The steady state concentration of $CH_3^{\cdot}$ in the reactor is then given by:

$$[CH_3]_{ss} = \frac{R_{CH_3}}{k_{eCH_3} + k_B(HI)_{ss}} \qquad (10.4)$$

where R_{CH_3} is the rate of production of CH_3 radicals in the reactor and k_B is the bimolecular rate constant for reaction with HI:

$$CH_3^{\cdot} + HI \xrightarrow{k_B} CH_4 + I \qquad (10.5)$$

The product CH_4 gives a mass spectrometer signal I_{CH_4}, given by:

$$I_{CH_4} = \alpha_{CH_4} k_{eCH_4} [CH_4]_{ss} = \alpha_{CH_4} R_{CH_4} \qquad (10.6)$$

but since $R_{CH_4} = k_B[CH_3]_{ss}[HI]_{ss}$:

$$I_{CH_4} = \alpha_{CH_4} k_B [HI]_{ss} [CH_3]_{ss} \qquad (10.7)$$

and from equation (8.4):

$$I_{CH_4} = \frac{\alpha_{CH_4} k_B [HI]_{ss} R_{CH_3}}{k_{eCH_3} + k_B [HI]_{ss}} \qquad (10.8)$$

The other stable product, acetone (Ac), can be used as a marker for the decomposition and $R_{Ac} = R_{CH_3}$. The signal of acetone is given by:

$$I_{Ac} = \alpha_{Ac} k_{eAc} [Ac]_{ss} = \alpha_{Ac} R_{Ac} = \alpha_{Ac} R_{CH} \qquad (10.9)$$

Hence, dividing equation (8.9) by equation (8.8):

$$\frac{I_{Ac}}{I_{CH_4}} = \frac{\alpha_{Ac}}{\alpha_{CH_4}} \left[1 + \frac{(k_{eCH_3}/k_B)}{[HI]_{ss}} \right] \qquad (10.10)$$

But $I_{HI} = k_{eHI}\alpha_{HI}[HI]_{ss}$, hence:

$$\frac{I_{Ac}}{I_{CH_4}} = \frac{\alpha_{Ac}}{\alpha_{CH_4}} \left[1 + \frac{(k_{eCH_3}/k_B) k_{eHI} \alpha_{HI}}{I_{HI}} \right] \qquad (10.11)$$

Equation (10.11) is a perfectly general equation which states that a plot of the ratio of the observed signals I_{Ac}/I_{CH_4} should, at a fixed temperature and for a given reactor, be a linear function of $(1/I_{HI})$, the reciprocal signal observed for HI. It doesn't matter what other reactions occur in the reactor, what fraction of the peroxide is decomposed, or how many of the *tert*-butoxyl radicals are themselves trapped by the HI.

Figure 7 shows a typical plot obtained for the reaction of $CH_3^{\cdot}$ with DBr following equation (10.11). The intercept in such a plot is simply the known ratio of calibration

[*] Inert carrier gas is frequently added to act as an internal standard for analytical calibration purposes. It is also useful (in 10- to 100-fold excess) for obtaining accurate flow measurements when working at very low flow rates.

factors $\alpha_{Ac}/\alpha_{CH_4}$, while the ratio of the intercept to slope will yield the desired rate constant k_B[*].

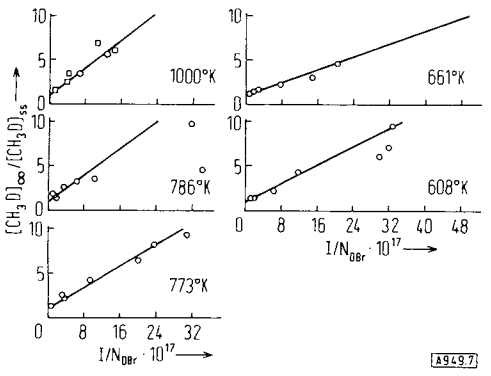


Fig. 7. "Titration" of $CH_3^\cdot$ with DBr.

The technique of the experiment is to establish a steady flow of peroxide and measure I_{CH_4} (should be zero), and I_{Ac}. HI is then introduced, and its flow progressively increased until (if possible) we have scavenged all CH_3 radicals, and we have obtained one CH_4 molecule for every acetone molecule. The same experiment is then repeated for enough different rates of flow of peroxide to make sure that the data are not flow dependent.

By such a method we could measure k_B for $CH_3^\cdot + DBr$ between 700 and 1100 °K and show that it was consistent with the known rate constant for the reverse reaction and the known thermochemical data for the species involved, including the CH_3 radical:

$$CH_3^\cdot + DBr \underset{-1}{\overset{1}{\rightleftarrows}} CH_3D + Br^\cdot \qquad (10.12)$$

$$K_1 = k_1/k_{-1} = \exp\{-\Delta G_1^0/RT\} \qquad (10.13)$$

We have also obtained data[**] by similar methods for the reactions of $CH_3^\cdot$ with HI, with NO_2, with I_2, for *tert*-BuO$^\cdot$ with HI, and with DBr, for *tert*-Bu$^\cdot$ with HI, and with DI.

Because of its great flexibility, VLPP has opened up an entirely new area for the hitherto almost inaccessible field of fast, radical-molecule reactions. Currently, we are investigating methods of atom production which will permit the direct study of fast atom-molecule reactions up to 1500 °K.

When radicals are being "titrated", as in the above experiment, those which do not react, escape. The escaping radicals can often be directly detected mass spectrometrically by lowering the ionizing voltage from the normal ≈ 70 eV to ≈ 10—13 eV. If we call the mass spectral intensity due to radicals at that voltage, I_R, then

$$I_R = \alpha_R k_{eR}[R] \qquad (10.14)$$

and the same sort of analysis as above indicates that for $CH_3^\cdot + HI$:

$$\frac{I_{Ac}}{I_{CH_3}} = \frac{\alpha_{Ac}}{\alpha_{CH_3}}\left[1 + \frac{I_{HI}k_B}{\alpha_{HI}k_{eHI}k_{eCH_3}}\right] \qquad (10.15)$$

Thus k_B can be measured from the slope and intercept of a plot of I_{Ac}/I_{CH_3} vs. I_{HI}.

11. Radical-Radical Reactions

Radical-radical reactions have been among the most difficult to study on an absolute basis. Until quite recently, the photochemical sector[30] method had been the only technique available for this study, and the results from it have been erratic—often in error by factors of from 10 to 10^3. In part, the difficulty lies in the problem of not knowing precisely the termination products of a chain reaction. Only for $CH_3^\cdot$ recombination has it given reliable results.

In VLPP only those gas-phase bimolecular processes which are rapid enough to compete with escape from the reactor occur. Given the lifetimes quoted earlier and the flow rates attainable, the rate constants for such processes have to be $\gtrsim 10^{6.5}$ lmol^{-1} s^{-1} ($Z = 2\times10^4$); $\gtrsim 10^{7.5}$ lmol^{-1}s^{-1} ($Z = 2\times10^3$); and $\gtrsim 10^{8.5}$ lmol^{-1} s^{-1} ($Z = 2\times10^2$).

These numbers generally limit the nature of these bimolecular processes to radical-radical and fast radical-molecule interactions, unencumbered with the complexities, such as chain reactions, which usually accompany them in the more conventional techniques.

In the event that the reaction studied is reversible, for example[31]

1,5-hexadiene (biallyl) (BA) $\underset{k_r}{\overset{k_1}{\rightleftarrows}}$ 2 allyl

equation (6.10) is modified and becomes

$$\frac{k_1}{k_{eba}} = \frac{F}{1 - 2K[BA]F} \qquad (11.1)$$

where $K = k_r/k_1$, and rearrangement gives

$$\frac{1}{F} = \frac{k_{eba}}{k_1} + 2K[BA]F \qquad (11.2)$$

thus a plot of $1/F$ vs. $[BA]F$ should be linear and k_1 is then obtainable from the intercept and K from the slope.

Even though both k_1 and k_r may not be the true high-pressure limiting rate constants, or even completely or in part heterogeneous, the principle of detailed balancing guarantees that the data will still give the true equilibrium constant K.

The pyrolysis of diallyl oxalate

Allyl—OCO—CO_2—allyl (DA) → 2 Allyl + 2CO_2

also generates allyl radicals, and the usual steady state treatment yields:

[*] α_{HI}, k_{eCH_3}, and k_{eHI} are known instrumental constants.

[**] Due to lack of time, much of this work has not been checked and so remains unpublished.

$$\frac{k_1}{k_1 + k_{eba}} = \frac{2k_{eba}^2[DA]}{2k_{eCO_2}[CO_2] - k_{eba}[DA]} \equiv Yk_{eba} \qquad (11.3)$$

Thus, as Y is an observable and k_{eba} is known, the left-hand side of (11.3) can be measured. Under conditions where $k_1 \gg k_{eba}$, this is equal to K.

The data which we obtained covered the temperature range 913 to 1063 K. By using both diallyl oxalate and biallyl as sources of allyl radicals, we were able to apply both equations (11.2) and (11.3). We obtained values for K, and also for ΔH and ΔS, in excellent agreement with previously measured values of ΔH and theoretically estimated values of ΔS.

Similar behavior has also been observed[10] in the high-temperature pyrolysis of ethyl benzene. Above 850 K this splits into $PhCH_2^{\cdot} + CH_3^{\cdot}$. At higher flow rates, one observes an apparent decrease in the first-order rate constant due to the recombination of $CH_3^{\cdot} + PhCH_2^{\cdot}$. Under these conditions, $2CH_3^{\cdot}$ will not recombine nor will $2PhCH_2^{\cdot}$. It is thus an ideal system for observing cross-combination.

The free radical R generated by the reaction:

$$RXR \xrightarrow{k_1} 2R + X$$

may react bimolecularly to combine (k_r) and/or disproportionate, (k_d), or it may "react" unimolecularly to escape. If R is the flow rate into the reactor of RXR, f is the fraction decomposed, and $k_{ea}[RXR]$ is the rate of escape of RXR through the reactor aperture, then we may write:

$$k_1[RXR] = R - k_{ea}[RXR] = fR \equiv T \qquad (11.4)$$

and from the above scheme, using $k_{er}[R]$ to denote the rate of escape of radicals R out of the reactor,

$$2T = 2(k_r + k_d)[R]^2 + k_{er}[R] \qquad (11.5)$$

Since $k_{er_2}[R_2] = k_r[R]^2 \equiv D$, where $k_{er_2}[R_2]$ is the rate of escape of R_2 from the reactor,

$$[R] = (D/k_r)^{1/2} \qquad (11.6)$$

Finally, combining equations (11.5) and (11.6) yields

$$\frac{T}{D} = \frac{k_r + k_d}{k_r} + \frac{k_{er}}{2k_r^{1/2}D^{1/2}} \qquad (11.7)$$

The quantities T and D are easily measured from intensities of the appropriately calibrated mass peaks as determined by the quadrupole mass spectrometer. Thus a plot T/D as a function of $(k_{er}D^{-1/2})$ should yield a straight line, the slope of which will be a measure of the rate constant for radical combination k_r and the intercept of which will thus yield k_d[*]. This procedure can be carried out at various temperatures, and the temperature dependence of k_r and k_d can be determined.

We have applied equation (11.7) to measurement of k_r for ethyl, isopropyl, and *tert*-butyl radicals obtained from various sources[32]. (The best source of radicals seems to be the azo compounds, the decomposition of which cleanly yields radicals with no measurable side reactions.) For any given aperture size, the Brauman plots are indeed linear, and their intercepts yield reasonable values for the ratio k_r/k_d. However, as illustrated in Figure 8 for *tert*-butyl radicals, a different straight line is obtained in reactors of different aperture size. The reason for this can be shown to be a wall catalyzed first-order loss of radicals, and at the time of this writing, reactors whose interior surfaces are coated with KCl are being used to eliminate the surface reaction.

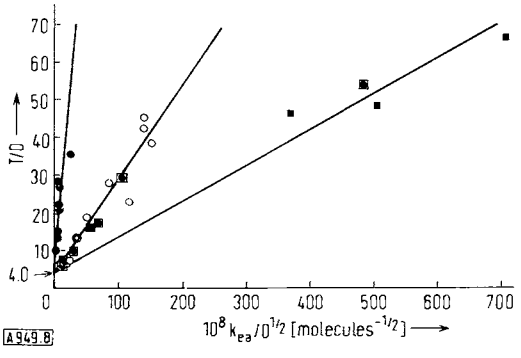


Fig. 8. Recombination of *tert*-butyl radicals, measurements in apparatus VLPP-I. $(k_r \cdot k_{r\infty})_{RRKM} = 0.96$; $k_d/k_{r\infty} = 3.1$; intercept from RRKM = 4.2; ·-●-●-·: $Z = 22400$, ·-○-○-·: $Z = 1920$, -■-■-: $Z = 280$; -⊡-⊡-: results with VLPP-II (volume corrected), $Z = 2000$.

It should also be noted that from three straight lines, such as depicted in Fig. 8, we can solve for a value of the first-order wall catalyzed rate constant k_w, since the effect on equation (11.7) is to change the numerator of the second term on the right-hand side to $(k_{er} + k_w)$.

Measurements at the time of writing, which must still be considered preliminary, yield the following values:

$k_{r\infty}$ (*tert*-butyl) $\approx 6 \times 10^8$ l mol^{-1} s^{-1} at 650 °K
$k_{r\infty}$ (isopropyl) $\approx 5 \times 10^9$ l mol^{-1} s^{-1} between 700 and 800 °K
$k_{r\infty}$ (ethyl) $\approx 10^{10}$ l mol^{-1} s^{-1} between 800 and 900 °K

There are some serious problems with these numbers, some of which may be resolved when they are measured at other temperatures. The values are too high compared to the accepted values[12] for the reverse processes and the overall values[12] of ΔH and ΔS.

12. Collisional Effectiveness in Vibrational Energy Transfer

The successful use of RRK(M) theory to relate k_1 to $k_{1\infty}$ for unimolecular reactions under VLPP conditions implies the correctness of the assumption used, namely that collisions of critically energized molecules with the reactor walls are 100 percent efficient in deenergizing same.

[*] Since the basic form for this equation was suggested by Professor *J. I. Brauman* of Stanford University during his sabbatical residence at Stanford Research Institute, we have come to call these plots "Brauman Plots".

If the flow rates used are increased to the point where the number of gas-gas collisions are comparable to the gas-wall collisions, always maintaining the condition that the mean-free path is large compared to the escape aperture, the increase in k_1 can be used as a measure of the effectiveness of gas-gas collisions compared to gas-wall collisions.

In the study of the pyrolysis of cyclobutane[14] the pressure dependence of the rate constant was measured at 969 °K. Individual RRKM curves were calculated according to the relation

$$k = \int_{E^*}^{\infty} \frac{P[E]k[E]}{1+k[E]/\omega_T} dE$$

where ω_T is the total collision efficiency. This can be written

$$\omega_T = \beta_s\omega_s + \bar{\beta}_g\omega_g$$

where β_s and $\bar{\beta}_g$ are relative collision efficiencies for gas-wall and gas-gas collisions, respectively. β_s was assumed to be unity and $\bar{\beta}_g$ is the average value for the different species under study. The experimental data are best fitted by the value $\bar{\beta}_g = 0.1$—0.2, and are the same for cyclobutane and SF_6. At the pressures used in this experiment k/k_∞ was about 0.08, and the effects of changing pressure should easily have been measured.

13. Surface Recombination of Atoms

The mechanism for surface catalyzed recombination of atoms is expected to be (S = surface site, assumed constant and surface diffusion neglected):

$$X + S \underset{-1}{\overset{1}{\rightleftarrows}} S{-}X \qquad (13.1)$$

$$X + S{-}X \xrightarrow{2} X_2 + S \qquad (13.2)$$

If $k_{-1} \gg k_2(X)$, the rate will be second order w.r.t. X. If, however, the reverse is true, it will be first order with a rate given by:

$$R_{X_2} = \frac{k_1k_2[X][S^0]}{k_1 + k_2} \equiv \gamma\omega[X] \qquad (13.3)$$

where ω is the collision frequency of atoms with the surface and the efficiency factor γ is called the recombination coefficient. No matter what the mechanism, the rate is always proportional to the total active surface.

If atoms are introduced into a multiple aperture VLPP reactor, the value of γ for the material of which the reactor is constructed can be ascertained from the change in mass spectral intensities of the atoms with change in aperture. When the rate of recombination is first order [eq. (13.3)], we find:

$$\gamma = \frac{(I'_X/I_X - 1)}{2Z_w[1 - I'_XZ'_w/I_XZ_w]} \qquad (13.4)$$

where I'_X and I_X are the intensities due to the atom in experiments using two different apertures, and Z'_w and Z_w are the collision numbers corresponding to these two apertures. Equation (13.4) results from comparison of the steady state concentrations of atoms as the aperture is changed (R_X being kept constant). Note that the measurements of γ together with R_{X_2} can be used to obtain absolute ionization efficiencies α_X of the species X.

We are currently measuring the values of γ for oxygen-atoms as a function of temperature for treated and untreated quartz surfaces.

14. Heterogeneous Reactions

The following studies have been carried out in our laboratories:

1. Reaction of oxygen with a carbonaceous char[33].
2. Pyrolysis of *tert*-BuO_2H in quartz and stainless steel reactors[34].
3. Pyrolysis of $CHCl_3$ in quartz reactors[23].
4. Pyrolysis of carbonylmetal compounds in a quartz reactor[35].
5. Pyrolysis of hydrocarbons in a special reactor capable of operating up to 1600 °C.

There are two basic categories of heterogeneous reactions. In the first, the gaseous reactant reacts directly with the substrate; in the second, the reactant is catalytically transformed into products. Of the studies that we have carried out so far, the pyrolysis of *tert*-BuO_2H[34] is probably the only example of true catalysis, although some details remain to be clarified in the case of the high-temperature reaction of ethane.

tert-Butyl hydroperoxide has been pyrolyzed in both quartz and stainless steel reactors[34]. The product pattern is dramatically different in the two cases. In the quartz reactor, the mechanism could be accounted for by the homogeneous reactions:

$$\textit{tert}\text{-}BuO_2H \rightarrow \textit{tert}\text{-}BuO^{\cdot} + OH^{\cdot}$$
$$\textit{tert}\text{-}BuO^{\cdot} \rightarrow CH_3^{\cdot} + (CH_3)_2CO$$

At higher pressures, isobutylene oxide is formed:

$$OH^{\cdot} + t{-}BuO_2H \rightarrow H_2O + \text{>}\!\!\!\diagup\!\!\!\diagdown\text{-}OOH \quad \text{(fast)}$$

$$CH_3^{\cdot} + t{-}BuO_2H \rightarrow \text{>}\!\!\!\diagup\!\!\!\diagdown\text{-}OOH + CH_4 \quad \text{(very slow)}$$

$$\text{>}\!\!\!\diagup\!\!\!\diagdown\text{-}OOH \rightarrow \text{<}\!\!\!\diagup\!\!\!\diagdown\text{O} + OH^{\cdot}$$

Isobutylene oxide, acetone, and lower mass number species were detected. The predicted Arrhenius parameters for the pyrolysis of the parent compound to yield acetone were in agreement with the observed reaction rate constant.

In the stainless steel reactor, the reaction rate was much faster and the mass spectrum of the product quite different.

The major product was *tert*-BuOH, although acetone and isobutene were also prominent. Isobutylene oxide is not produced. We infer that the reaction in the metal system is catalyzed by surface oxides of iron, chromium or nickel. The proposed mechanism was:

$$tert\text{-}BuO_2H(g) \underset{-1}{\overset{1}{\rightleftarrows}} tert\text{-}BuO_2H(s)$$

$$tert\text{-}BuO_2H(s) + O^{2-}(s) \xrightarrow{2} tert\text{-}BuO_2^-(s) + OH^-(s)$$

or

$$tert\text{-}BuO_2H(s) + O^{2-}(s) \xrightarrow{3} tert\text{-}BuO^-(s) + HO_2^-(s)$$

Products arise from decomposition and further reaction of the surface species. Details remain speculative. The temperature at which reaction occurs suggests that the surface reactions have a slightly higher activation energy than reevaporation, $k_2+k_3<k_{-1}$. A value of about 21 kcal was suggested for the above surface reactions.

The internal surfaces of the reactor showed no changes in color as a consequence of reactions of *tert*-BuO_2H. We conclude that the reaction was one of almost pure catalysis.

It is specially noteworthy that the "much" slower (because of its endothermicity of ≈ 14 kcal/mol) surface-catalyzed dehydration of *tert*-BuOH to *i*-$C_4H_8 + H_2O$ did not occur.

The reaction of oxygen gas with carbonaceous chars has also been studied in our VLPP systems[33,35]. We have prepared charry carbonaceous surfaces in the form of thin films by pyrolysis of an epoxy resin film. The samples in the form of coatings on the inside surface of a quartz cylinder were inserted into a VLPP reactor and reacted with oxygen gas at temperatures up to 1300°K.

The reactivity of these films is a complex function of the chemical history of the sample. At first, reactivity is relatively low; then, as the surface of the sample burns away, it becomes more active. In addition to this, a greater amount of surface area is available for reaction. As reaction proceeds, the film becomes exhausted and the rate of reaction declines to zero. The rate "constant" varies with temperature in approximate agreement with the Arrhenius equation. The major reaction product at all temperatures is CO with about 10% CO_2. The reaction is lower than first order in oxygen. This deviation from first-order behavior is less pronounced at gas flows of 10^{14} per second than at 5×10^{16} per second for a char of superficial area 36 cm^2. Exposure to the atmosphere can deactivate the char.

In our initial studies with this system[33] we reported first-order rate constants about 10^5 faster than those observed in similar studies with graphites + O_2. Later, incomplete[35] studies showed that these fast rates were the result of an astonishingly rapid catalytic oxidation produced by the presence of a stainless steel endplate in the system. An all-quartz vessel gave much slower rates with lower O_2 dependence. This is an interesting result with much potential importance for the study of catalytic oxidation.

The pyrolysis of $Mo(CO)_6$ indicates[35] that a surface chain reaction takes place. Apparent first-order rate constants for the disappearance of $Mo(CO)_6$ change from *ca.* 2 s^{-1} at 473°K to *ca.* 500 s^{-1} at 526°K, leading to an activation energy of *ca.* 50 kcal/mol and an *A*-factor of *ca.* 10^{24} s^{-1}. The high *A*-factor is indicative of a chain reaction.

Hydrocarbon gases have been pyrolyzed[36]. Gases such as ethane, ethylene, and benzene have been found to react with high probability (>0.005 per collision) at temperatures above 1600°K. Reactor walls participate in the chemical reaction. For example, carbon monoxide is copiously evolved when benzene or toluene react in an alumina reactor; carbon monoxide is also a significant product when pyrolysis is carried out in a quartz reactor.

Ethane is significantly less reactive than the unsaturated compounds in quartz, alumina, and carbon reactors.

15. Summary

The technique of VLPP is well established as a method for measuring unimolecular rate constants. These data, in conjunction with RRK(M) theory, can yield high-pressure activation energies if reasonable estimates of activation entropy can be made. This is a useful method for obtaining the heats of formation of free radicals formed in a unimolecular bond homolysis, as well as activation energies for some important concerted processes.

The general applicability of VLPP as a tool for the measurement of rapid bimolecular reactions is currently being assessed. In this type of application, VLPP yields important rate parameters for radical-molecular and radical-radical reactions. The extension to reactions of atoms is also being investigated.

Experiments carried out at pressures such that gas-gas collisions begin to compete with gas-wall collisions can be used to measure the relative effectiveness of walls and gases in the transfer of vibrational energy in the study of unimolecular reactions in the "fall-off" region of pressures.

The system lends itself very well to the study of fast heterogeneous reactions; that is, both on "inert" surfaces and on chemically active surfaces. In such systems it gives unique information not otherwise available. The system lends itself very well to the direct observation of the chemistry and kinetics of chemically active species such as atoms and radicals.

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The Physical Mechanism of the Chemical Bond[1]

By Werner Kutzelnigg[*]

First the interplay of kinetic and potential energy *via* the uncertainty relation is described with the aid of a variational function for the ground state of the H atom. The H_2^+ ion is used to illustrate the physical mechanism of the occurrence of the chemical bond. The formation of the chemical bond can be divided into three steps: 1. the quasi-classical (electrostatic) interaction of the unchanged electronic charges of the separate atoms; 2. the interference of the atomic orbitals, which (in the case of positive interference) leads to a displacement of charge into the bonding region and to a decrease in the kinetic energy; 3. deformation of the molecular orbitals to restore the correct balance of kinetic and potential energy. In simple models, it is often sufficient to consider just the second step. A two-electron bond is not fundamentally different from a one-electron bond. In larger molecules it is possible to distinguish between long-range and short-range interatomic contributions to the chemical bond. If the former are small, *i.e.* in molecules with non-polar bonds, a one-electron molecular orbital theory can be justified. Finally, the possibility of describing molecules by localized bonds is discussed.

1. Introduction

The first publication to deal with the theory of the chemical bond on a quantum-mechanical basis appeared in 1927[2], *i.e.* 46 years ago. One cannot deny nowadays that quantum chemistry has had a lasting influence on chemistry as a whole, though it was accepted only reluctantly during its first few decades.

There is nevertheless still an extremely wide gap between descriptive theoretical chemistry used in chemistry textbooks and computational quantum chemistry of present-day research. Many concepts from the early days of quantum chemistry that have found their way into the descriptive theory have become insignificant or useless in current

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quantum-chemical research. It often seems that even the chemical bond itself is one such concept. Ideas about binding patterns are not necessary input for the calculation of the properties of a molecule from approximate solutions of the Schrödinger equation. Such ideas become relevant only when one attempts to gain a physical understanding of the results of the calculation, or even to make significant statements about the molecule without calculation.

In the early phase of quantum chemistry, calculation and interpretation went hand in hand, and the theory was fed more with material from chemical experience than with information from the Schrödinger equation; the results of quantum-chemical research during the past 20 to 30 years, on the other hand, have had little effect on theoretical chemistry as taught in chemistry textbooks. Many obsolete ideas were thus obstinately adhered to in the textbooks. Attempts have in fact been directed toward a deductive theory of the chemical bond whose predictions should not depend either on the nature of the approximation chosen or on the current state of chemical experience[3, 4], but access to these is probably too difficult for the uninitiated. In the present article we shall try to explain some aspects of a modern theory of the chemical bond.

In particular, an effort will be made to clarify the physical mechanism of the occurrence of chemical binding. If more reference is made to H_2^+ than to molecules that are more familiar to the chemist, the reason is that the decisive mechanism can in fact be understood from this molecule-ion.

The reader will appreciate that the fact that a question is asked does not mean that its answer is known. The question of the nature of the chemical bond has by no means been fully clarified.

2. Kinetic and Potential Energy in the H Atom

Atoms and molecules are systems of masses (nuclei and electrons) between which there is Coulomb attraction or repulsion, and which move according to the laws of quantum mechanics. As in macroscopic systems, for example a planetary system, the concepts *kinetic energy T*, *potential energy V*, and *total energy* $E = T + V$ are found to be useful for the description of the system.

Let us consider the motion of an electron (of charge $-e$ and mass m) about a proton, which we shall assume to be at rest. Let r be the distance between the electron and the nucleus. Let v be the velocity and $p = mv$ the momentum. The kinetic energy T and the potential energy V (Coulomb's law) are then given by

$$T = \frac{m}{2} v^2 = \frac{1}{2m} p^2; V = -\frac{e^2}{r} \tag{2.1}$$

In a system of Cartesian coordinates with the proton at the origin, according to Pythagoras

$$r = +\sqrt{x^2 + y^2 + z^2} \tag{2.2}$$

where x, y, and z are the coordinates of the electron.

The concepts used above retain their meaning in quantum mechanics, with the limitation (which we shall discuss later) that neither the position nor the momentum is accurately known, since these two parameters are subject to *Heisenberg*'s uncertainty principle. For example, if Δx is the uncertainty of the x coordinate and Δp_x the uncertainty of the component p_x of the momentum in the x direction, the product of these uncertainties cannot be reduced indefinitely, but is governed by

$$\Delta x \cdot \Delta p_x \approx \hbar \tag{2.3}$$

($h = 2\pi\hbar$ is Planck's action quantum).

Because of the uncertainty regarding the location of the electron, we do not know where the electron is situated, but can only give a probability distribution $\rho(x,y,z)$ for its position. $\rho(x,y,z)$ is also known as the electron density, and

$$\rho(x,y,z)\, dx dy dz = \rho(x,y,z)\, d\tau \tag{2.4}$$

is the probability of finding the electron in a volume element $d\tau$ in the position x,y,z. Since there should be a total of one electron present, the total probability must be equal to 1, *i.e.*

$$\int \rho(x,y,z) d\tau = \int_{-\infty}^{+\infty} \iint \rho(x,y,z)\, dx dy dz = 1 \tag{2.5}$$

For a one-electron system the electron density is equal to the square of the magnitude of the wave function

$$\rho(x,y,z) = |\psi(x,y,z)|^2 \tag{2.6}$$

The wave function of the ground state of the H atom is given by

$$\psi = N \cdot e^{-r} \tag{2.7}$$

where r is measured in atomic units of length a_0 ($1\, a_0 = \hbar^2/me^2 = 0.523$ Å) and N is a normalizing factor[5], which ensures that (2.5) is satisfied.

Let us now suppose we do not know that the wave function of the ground state of the H atom is equal to $N \cdot e^{-r}$ and assume simply that it is an exponential function; we therefore introduce an undetermined factor η into the exponent, *i.e.* we let

$$\psi = N \cdot e^{-\eta r} \tag{2.8}$$

(The normalizing constant N then also depends on η[5], but we are not interested in the explicit dependence at the moment.) Figure 1 shows $|\psi|^2$ as a function of r for various η (since the ordinate is logarithmic, $|\psi|^2$ is a straight line in every case). We interpret $|\psi(r)|^2$ as $|\psi(|x|)|^2$ for $y = 0$ and $z = 0$, *i.e.* as the electron density along the x axis. We should then also consider the mirror image of Figure 1 reflected in the ordinate, since $|\psi(|x|)|^2$ has the same value for $+x$ as for $-x$.

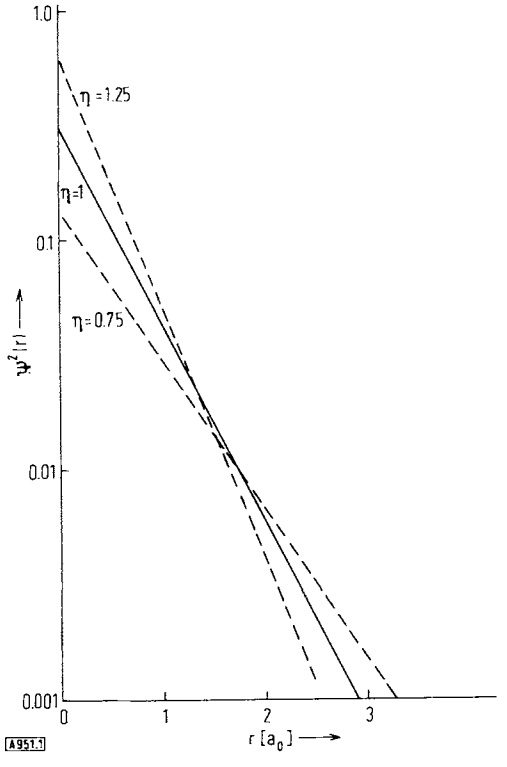


Fig. 1. Electron density $\psi^2(r)=N^2\cdot e^{-2\eta r}$ of the atom for various orbital exponents η.

Since positive and negative values of x are equally probable, the mean $\langle x\rangle$ of x is equal to zero[6] (the symbol $\langle f\rangle$ is used for the mean of a quantity f over the distribution given by ρ).

The extent to which the electron is located close to the nucleus, on average, is determined by the uncertainty[7] of its distribution. The greater η, the steeper is $|\psi^2|$ (Fig. 1), the smaller therefore is the uncertainty regarding its location, and the greater is the probability of finding the electron in the vicinity of the nucleus. An explicit calculation gives the following expression for the uncertainty of the x coordinate (for $y=z=0$; similar expressions are found for the uncertainty of the y and of the z coordinates)

$$\Delta x = \frac{1}{\eta}\cdot a_0 \tag{2.9}$$

The positional uncertainty is thus inversely proportional to η[7].

What influence has η on the potential energy V? The greater the value of η, the greater is the probability, on average, of finding the electron in the vicinity of the nucleus. Since $V=-e^2/r$, the greater η and the smaller therefore the mean distance $\langle r\rangle$ of the electron from the nucleus, the greater is $|\langle V\rangle|$, *i.e.* the lower (more negative) is $\langle V\rangle$, the mean of the potential energy.

An accurate calculation gives

$$\langle V\rangle = -\eta \text{ a.u.} \tag{2.10}$$

if the atomic unit (1 a.u.=1 Hartree$=m\cdot e^4/\hbar^2=627.2$ kcal/mol) is taken as the unit of energy.

How does the kinetic energy T vary with η? For the answer to this, let us consider the uncertainty principle. The greater the value of η, the greater is the average probability of finding the electron in the vicinity of the nucleus, *i.e.* the more it is localized and the smaller is its positional uncertainty. With increasing η, therefore, the uncertainty of momentum must increase, and higher momenta become more probable, *i.e.* the kinetic energy increases. Figure 2 shows the probability distribution of the momentum for various values of η, which demonstrates more precisely the results of our qualitative considerations[8].

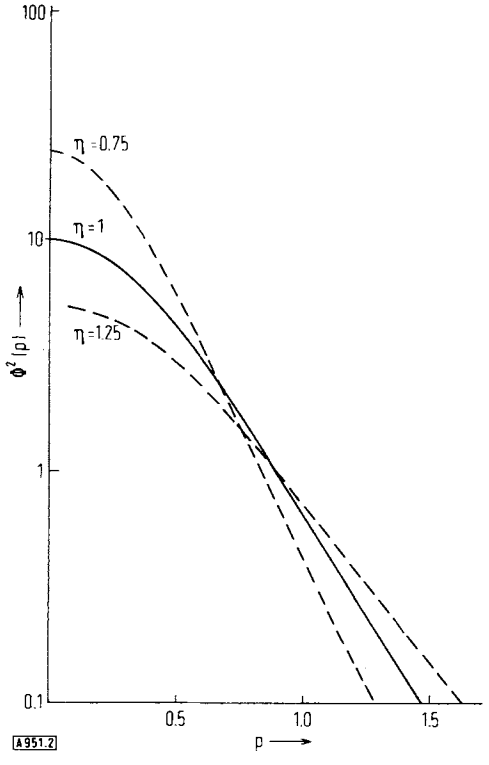


Fig. 2. Momentum distribution $\phi^2(p)$ corresponding to $\psi(r)=N\cdot e^{-\eta r}$ for various values of η.

The mean $\langle p_x\rangle$ of the x component of the momentum vanishes for the same reason as $\langle x\rangle$. For the uncertainty Δp_x, calculation gives

$$\Delta p_x = \frac{1}{\sqrt{3}}\cdot\eta\cdot\frac{\hbar}{a_0} \tag{2.11}$$

which, together with (2.1) and (2.9) shows in fact that the product $\Delta p\Delta p_x$ is independent of η and is of the order of magnitude $\hbar$. The mean of the kinetic energy is proportional to the square of the uncertainty in the momentum

$$\langle T\rangle = \frac{1}{2}\eta^2 \text{ a.u.} \tag{2.12}$$

$\langle T\rangle$, $\langle V\rangle$, and $E=\langle T\rangle+\langle V\rangle$ are shown in Figure 3 as functions of η. We see that E has a minimum for $\eta=1$ and that the following relation is accurately satisfied at the position of the minimum:

$$E=\langle V\rangle+\langle T\rangle=-1+\frac{1}{2}=-\frac{1}{2}\text{ a.u.} \tag{2.13}$$

In the ground state, an atom or molecule assumes the *lowest* possible energy as a compromise between the lowest possible potential energy (large in magnitude, since $\langle V \rangle$ is negative) and the lowest possible kinetic energy (small in magnitude, since $\langle T \rangle$ is positive). A large η (steep function) is more favorable from the standpoint of the potential energy and a small η from the standpoint of the kinetic energy, the best compromise being $\eta = 1$.

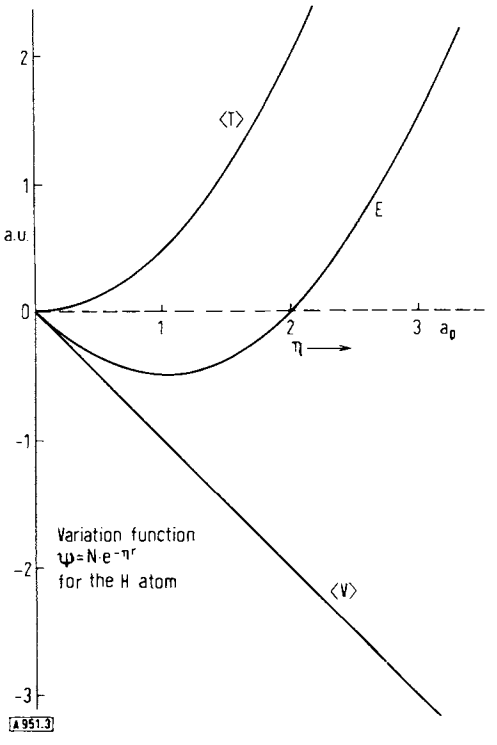


Fig. 3. Kinetic energy $\langle T \rangle$, potential energy $\langle V \rangle$, and total energy E as a function of η.

It can be shown (though we shall not pursue this here) that the energy value for the H atom cannot be reduced below -0.5 a.u. even by variations of the wave function other than variation of η (*e.g.* by modification of the functional form of ψ), *i.e.* that -0.5 a.u. is the *absolute* minimum of the energy of an H atom. According to the variation principle, a wave function that makes the energy an absolute minimum is automatically a solution of the Schrödinger equation for the ground state of the system in question.

The fact that an atom or molecule has a ground state, *i.e.* that there is a limit to the degree to which the energy can become negative, is a direct consequence of the relationship of $\langle T \rangle$ and $\langle V \rangle$ *via* the uncertainty principle. In classical physics, there is no lowest possible energy and there is no limit to how close the orbital curve lies to the nucleus, whereas in quantum mechanics the kinetic energy ensures that this is not possible[9].

$$\langle T \rangle = -E = \frac{1}{2} \text{a.u.} \tag{2.14}$$

This relation between $\langle T \rangle$ and E is generally valid for systems with Coulomb interactions, and is known as the *virial theorem*. We shall make use of this again later.

3. The H_2^+ Ion. Quasi-Classical Interaction and Interference

Let us now proceed from the simplest atom, H, to the simplest molecule, H_2^+. This molecule consists of two protons and one electron (Fig. 4). In order to understand the chemical bond in this molecule-ion, we shall build up H_2^+ in steps, starting with an isolated H atom and a proton.

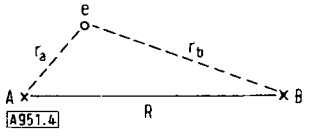


Fig. 4. Distances in the H_2^+ ion.

Let a be the wave function (atomic orbital) of an H atom centered on the first proton, and b that of an H atom centered on the second proton.

$$\begin{aligned} a &= N \cdot e^{-r_a} \\ b &= N \cdot e^{-r_b} \end{aligned} \tag{3.1}$$

The electron density of an electron that forms an H atom with the nucleus A would thus be a^2, and that of an electron about the nucleus B would be b^2. If we assume that the electron has equal probabilities of belonging to the nucleus A and to the nucleus B, we can deduce that the electron density in H_2^+ should be given by[10].

$$\rho_{QK} = \frac{1}{2}[a^2 + b^2] \tag{3.2}$$

The subscript QK of ρ denotes "quasi-classical"; the above argument will be described as quasi-classical, by which we mean that we simply add the electron densities of the atoms participating in a bond, without taking into account any change in the electron density as a result of bonding[11].

This quasi-classical description of the H_2^+ ion (or of another molecule) is only a first step on the way from the separate atoms to the molecule.

We shall first examine the magnitude of the energy of an H_2^+ if its electron density is given by ρ_{QK}.

The energy of this quasi-classical H_2^+ is found to be identical with that of an H atom plus that of a proton at a distance R[12].

$$E_{QK} = E(\text{H}) + \frac{e^2}{R} - E_{Ke} \tag{3.3}$$

$$E_{Ke} = \int e^2 \frac{|a(r_a)|^2}{r_b} \, d\tau \tag{3.4}$$

The first term in (3.3) is simply the energy of an H atom ($= -0.5$ a.u.), while the other two terms depend on R. For large values of R, E_{Ke} is almost equal to e^2/R, so that the last two terms in (3.3) cancel out for large R. For shorter distances E_{Ke} is equal to the Coulomb interaction of the nucleus B with that part of the charge of

the electron that is situated inside a sphere around the nucleus A whose surface passes through the nucleus B[13]. For $R \rightarrow 0$, E_{Ke} tends toward a finite value, while the internuclear repulsion e^2/R becomes infinite. The internuclear repulsion predominates at short distances.

As a consequence of the *penetration* of the nucleus into the electron cloud, the overall result is a repulsion that is purely electrostatic. Detailed evaluation of the quasi-classical H_2^+ gives (in atomic energy units)

$$E_{QK} = -\frac{1}{2} + \left(1 + \frac{1}{R}\right) e^{-2R} \tag{3.5}$$

From a comparison of E_{QK} with the true energy of H_2^+ (Fig. 5), it is clear that we have failed to reproduce the energy minimum that is decisive for the occurrence of bonding.

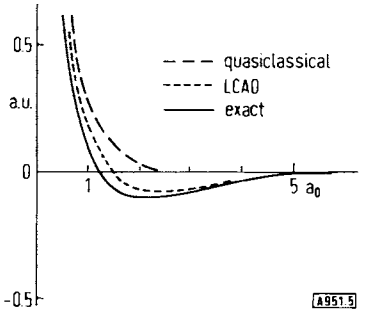


Fig. 5. H_2^+ potential energy curve.

What have we done wrong? Our quasi-classical argument would be analogous to superimposing two light beams by simply taking the sum of the individual intensities as the total intensity. The intensity of a light beam is equal to the square of its amplitude, just as the electron density is the square of the wave function. We know that we must in fact add the *amplitudes* of the light waves, and that the effects associated with the fact that addition of the amplitudes does not give the same result as addition of the intensities are known as *interference*.

If we take the wave nature of the electron seriously, we should add wave functions in this case instead of densities, *i.e.* in addition to the quasi-classical effects, we shall also have to consider interferences. Let us now examine these more closely.

The atomic orbitals (AOs) a and b are known except for the sign. Addition of these orbitals can give both $(a+b)$ and $(a-b)$, so that we have the possibility of positive and negative interference. $(a+b)$ or $(a-b)$ should be a wave function for an electron, *i.e.* we require these wave functions to be normalized to 1; for example

$$\begin{aligned} \int \psi_+^2 \, d\tau &= N^2 \int (a+b)^2 d\tau = N^2 \int [a^2 + 2ab + b^2] d\tau \\ &= N^2 \{\int a^2 d\tau + \int b^2 d\tau + 2\int ab \, d\tau\} \\ &= N^2 \{1 + 1 + 2S\} = 1 \end{aligned} \tag{3.6}$$

We have taken into account here the fact that a and b are each normalized to 1, and we call the integral

$$\int ab \, d\tau = S \tag{3.7}$$

the "*overlap integral*" between a and b.

It follows directly from (3.6) that

$$N = \frac{1}{\sqrt{2(1+S)}} \tag{3.8}$$

i.e. that in the case of positive interference, the wave function of H_2^+ is

$$\psi_+ = \frac{1}{\sqrt{2(1+S)}} [a + b] \tag{3.9}$$

The corresponding electron density is then

$$\rho_+ = \psi_+^2 = \frac{1}{2(1+S)} [a+b]^2 = \frac{1}{2(1+S)} [a^2 + b^2 + 2ab] \tag{3.10}$$

Let us compare this electron density with that derived from our quasi-classical considerations.

$$\rho_{QK} = \frac{1}{2} [a^2 + b^2] = \frac{1}{2(1+S)} [a^2 + b^2 + Sa^2 + Sb^2] \tag{3.11}$$

$$\Delta\rho = \rho_+ - \rho_{QK} = \frac{1}{2(1+S)} [2ab - Sa^2 - Sb^2] \tag{3.12}$$

This change $\Delta\rho$ in the electron density distribution as a result of the interference is of the following nature. Where a and b are both large, the electron density is increased because of the contribution $2ab$; where only a or only b is large, the electron density decreases. Electronic charge is transferred from the vicinity of the nuclei into the bonding region. This change in the electron density along the line joining the nuclei is illustrated in Figure 6.

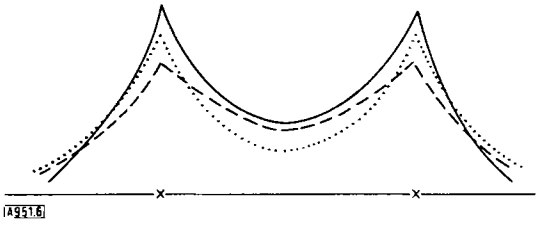


Fig. 6. Schematic representation of the quasi-classical electron density (...) and the quantum-mechanical electron density without promotion (---) and with promotion of the AOs (—) in the H_2^+ ion.

The inclusion of this interference effect in the argument does in fact lead to a decrease in energy, to a minimum in the potential curve, and hence to chemical bonding (cf. Fig. 5).

Now comes the critical question. What physical mechanism is responsible for the fact that the (positive) interference of the atomic orbitals leads to a decrease in energy and hence to bond formation? Nearly all textbooks give an incorrect answer to this question.

It is claimed that the accumulation of charge in the bonding region causes a decrease in the potential energy, since the electron is then situated preferentially in a region in which it is attracted simultaneously by both nuclei. This

corresponds to saying that the interference produces *additional* electron density, *i.e.* it is completely forgotten that this electron density must be taken from somewhere else, since the total number of electrons is not affected by the interference. However, if one considers that the phenomenon is really only a displacement of charge, one finds that electron density is removed from places that are much more favorable to the potential energy, particularly in the immediate vicinity of a nucleus. The interference actually leads to a slight increase in the potential energy, and not to a decrease.

Thus if a change in the potential energy is not responsible for bonding, the decisive factor can clearly only be the kinetic energy.

This is in fact considerably reduced by the interference. *Hellmann*[14], in 1933, was probably the first to recognize this fact, for which he also gave an intuitive explanation (possibly oversimplified, but essentially correct). The transition from the separate atoms to the molecule increases the space available to the electrons (the electron in this case), *i.e.* the positional uncertainty increases. However, an increase in the positional uncertainty implies a decrease in the uncertainty of the momentum. Since the average momentum is zero, smaller momenta become more probable overall, *i.e.* the kinetic energy becomes smaller.

How was the evidently incorrect explanation of the chemical bond (it was said to be based on a decrease in the potential energy, and thus to be electrostatic in nature) able to persist for so long? One reason is undoubtedly a widespread carelessness in dealing with overlap integrals. Thus it is common to proceed as if S could be neglected. It then appears indeed as if

$$\rho_+ = a^2 + b^2 + 2ab = \rho_{QK} + 2ab \tag{3.13}$$

i.e. as if there were a "spontaneous generation" of charge in the bonding region. There is much that could be said on the topic of "neglect of overlap"[15]. We shall content ourselves here with expressing our sympathy for those who feel duped when (as often occurs) they are first taught that overlap is the decisive reason for the occurrence of chemical bonding, and are then told two lectures later that the overlap integral can be disregarded.

A second reason why the incorrect explanation of chemical bonding was able to persist is the widespread partiality in chemistry for electrostatic models, which is apparently justified (but only apparently) by the Hellmann-Feynman theorem[16]. The idea that the kinetic energy of the electrons in the molecule plays a decisive part evidently meets with certain difficulties of visualization.

There is also a third reason. This is connected with the virial theorem and an impermissible amalgamation of the approximate solution and the exact solution of the Schrödinger equation. It will be necessary to consider this more fully.

What we have just seen is that the interference of the atomic orbitals has practically no influence on the potential energy, but that it reduces the kinetic energy and so leads to bonding.

We must remember, however, that the wave function (3.9) formed by linear combination of the atomic orbitals (abbreviated to LCAO) is an approximate wave function of H_2^+ and not the exact wave function, and that it undoubtedly differs in some way from the exact wave function.

Actually the virial theorem is applicable for the exact wave function of a diatomic molecule at the equilibrium distance in the same form as for atoms (cf. Section 2, (2.14))

$$\langle T \rangle = -E \tag{3.14}$$

If the virial theorem is valid, however, the following argument is straightforward. The occurrence of bonding means that the energy of the molecule is greater in magnitude than the sum of the energies of the separate atoms.

$$|E_{\text{mol.}}| \geq |E_{\text{sep. at.}}| \tag{3.15}$$

Since the virial theorem (3.14) is valid both for the molecule and for the separate atoms and since $\langle T \rangle$ is always positive, one obtains

$$\langle T \rangle_{\text{mol.}} \geq \langle T \rangle_{\text{sep. at.}} \tag{3.16}$$

In other words, the kinetic energy of the molecule is greater than that of the separate atoms.

On the basis of the virial theorem, therefore, some authors[17] have tried to extend the Hellmann picture of chemical bonding *ad absurdum*. However, they were defeated by a fallacy. The elucidation of this fallacy was due in particular to *Ruedenberg*[4, 18].

Since the interference of the AOs leads to a decrease in the kinetic energy, whereas in the exact wave function of the H_2^+ ion the kinetic energy is greater than in the H atom, something else must happen on the way from our approximate solution to the exact solution. In other words, in addition to the two contributions discussed so far, *i.e.* quasi-classical interaction and interference, a third contribution to the chemical bond must also be present. However, this contribution is less important than the first two, since these have already led to a fairly good potential curve.

To understand what such a third step signifies, let us make use of an apparently far-fetched analogy. Let each of two business concerns have receipts ($-V$), expenditures (T), and profit ($-E$). Suppose that a concern operates most rationally when the ratio of expenditures T to profit E has a certain value, and assume for simplicity that the optimum ratio is such that

$$\text{expenditures } (\langle T \rangle) = \text{profit } (-E) \tag{3.17}$$

(virial theorem). Now suppose that the two concerns merge. Certain expenditures that each concern previously had to bear separately are now necessary only once. The total expenditure $\langle T \rangle$ decreases, with the result that the profit E automatically increases. ("Bonding" occurs.) However the ratio $\langle T \rangle : (-E)$ is no longer 1:1, *i.e.* no longer corresponds to optimum profitability, since T had become smaller and E larger. A *further* increase in profit is therefore possible

if the joint concern undertakes additional expenditures that did not pay in the case of a single concern. A superficial observer would now say that expenditures and receipts increased after the amalgamation, the receipts to a greater extent, so that the increased profit is due to an increase in receipts. This commentator completely overlooks the fact that the decisive step toward the increase in profits was the saving of certain expenditures.

How does this argument apply to the theory of chemical bonding?

Once interference of the AOs and the associated decrease in kinetic energy has led to bonding, the ratio of kinetic to potential energy for the molecule is no longer optimum; the positional uncertainty has become too great and the uncertainty of momentum too small. We cannot therefore have reached the energy minimum for the molecule in this way.

We can see how we can at least come closer to this aim if we apply what we learned for the H atom. We introduced a variable factor η into the exponent in the LCAO function.

$$\psi_+ = \frac{N}{\sqrt{2(1+S)}}\left[e^{-\eta r_a} + e^{-\eta r_b}\right] \tag{3.18}$$

Let us again consider the influence of variation of η on the potential and kinetic energy. The most favorable "compromise η" is now found to be $\eta = 1.25$ (different from the value of $\eta = 1$ for the H atom). The electron density (cf. Fig. 5) becomes steeper in the vicinity of the nucleus, the positional uncertainty decreases, and the uncertainty of momentum and the kinetic energy increase; the positional uncertainty is decreased mainly *perpendicular* to the bond direction, and is actually increased along the bond direction as a result of bonding. The kinetic energy of the motion normal to the bond direction increases accordingly; along the bond direction, however, the decrease in kinetic energy due to interference predominates. An important point in any case is that the increase in the kinetic energy and the decrease in the potential energy as a result of the variation of the exponential factor η is purely *intra-atomic* and has nothing to do with what happens in the bonding region, where the decrease in the kinetic energy is still the decisive effect. One can also say that the molecule is slightly compressed normal to the bond direction, and the resulting increase in the kinetic energy ensures that the virial theorem is satisfied.

We have just broken down the occurrence of bonding into three steps, *i.e.* a first "quasi-classical" step, a second step in which the atomic orbitals of the free H atoms are caused to interfere, and a third step in which we restored the balance of the positional uncertainty and the uncertainty of momentum in the molecule. The same result is obtained if the order of the last two steps is reversed:

1. We change the atomic orbitals of an H atom into atomic orbitals with $\eta = 1.25$, *i.e.* we prepare them, so to speak, for bonding. We thus increase the kinetic energy and decrease the potential energy without essentially changing the total energy of the H atom. The quasi-classical interaction of the promoted AOs is not qualitatively different from that of the unprepared orbitals.

2. The two atomic orbitals "prepared" ("promoted") for bonding in this way are allowed to interfere. Charge is thus displaced into the bonding region, and the kinetic energy changes in the bonding region.

This order of the steps, though just as arbitrary as that described earlier, is possibly somewhat clearer and more suggestive, particularly since the idea of preparation (promotion) of the atoms for bonding is also useful in another connection.

To summarize, therefore, we find three contributions to the bond energy in H_2^+:

1. The *quasi-classical interaction* of the nuclei and of the electron density distributions of the "unbound" atoms. This interaction is only repulsive, but the repulsion (as a result of the penetration into the electron shell) begins only at very short distances.

2. The *interference*. This may be additive (constructive) or subtractive (destructive). We have considered only the case of additive interference. This leads to a displacement of charge from the vicinity of the nucleus into the region between the nuclei (in the opposite direction in the case of negative interference). The charge displacement is accompanied by a decrease in kinetic energy, which causes bonding (or in the case of negative interference an increase in kinetic energy and hence repulsion).

3. *Deformation* of the atomic orbitals. This is essentially a contraction here[19]; the AOs adapted to the molecule are more localized in the vicinity of the nuclei. A change in the AOs on molecular formation is generally referred to as "promotion" or conversion into the valence state. In the case of H_2^+, the promotion leads only to a change in the balance of the intra-atomic potential and kinetic energies; it has substantially no influence on the binding energy. However, it is important to the correct behavior of the wave function at small internuclear distances (this will not be discussed here).

As was stressed this third contribution is less important than the first two. It is therefore often disregarded, with some justification. Considerations based on the virial theorem naturally have no place in models of the chemical bond in which the third step is disregarded.

4. Models of the One-Electron Bond

So far we have encountered three contributions to the chemical bonding in H_2^+. However, to describe the bonding as simply as possible while still at least qualitatively retaining the essential points, one may consider only the contribution due to interference. The quasi-classical repulsion in the neighborhood of the minimum is in fact extremely small (cf. Fig. 5), so that while disregarding the quasi-classical term seriously affects the potential curve at short distances, it has little influence in the vicinity of the minimum. Disregarding the promotion changes the potential curve only quantitatively but not qualitatively.

Let us therefore confine ourselves entirely to the interference contribution. The charge displacement due to interference

$$\Delta\rho_+ = \frac{1}{2(1+S)}\{2ab - Sa^2 - Sb^2\} \tag{4.1}$$

is associated with an energy change consisting of a change in the kinetic and in the potential energy.

$$\Delta E_+ = \Delta\langle T\rangle + \Delta\langle V\rangle \tag{4.2}$$

Both $\Delta\langle T\rangle$ and $\Delta\langle V\rangle$ consist of contributions corresponding to the breakdown of $\Delta\rho$ in accordance with (4.1)

$$\begin{aligned}\langle T\rangle &= \frac{1}{2(1+S)}\{2T_{ab} - ST_{aa} - ST_{bb}\}\\ \Delta\langle V\rangle &= \frac{1}{2(1+S)}\{2V_{ab} - SV_{aa} - SV_{bb}\}\end{aligned} \tag{4.3}$$

where V_{ab} is the mean of the potential energy $-e^2/r$ calculated with the charge density a b, and V_{aa}, V_{bb}, T_{ab}, T_{aa}, and T_{bb} are defined analogously. Since, because of the equivalence of a and b, we apparently have

$$\begin{aligned}T_{aa} &= T_{bb}\\ V_{aa} &= V_{bb}\end{aligned} \tag{4.4}$$

with

$$\begin{aligned}H_{ab} &= T_{ab} + V_{ab}\\ H_{aa} &= V_{aa} + T_{aa} = E(\mathrm{H})\end{aligned} \tag{4.5}$$

we can also write

$$\Delta E_+ = \frac{1}{1+S}\{H_{ab} - S\cdot E(\mathrm{H})\} = \frac{1}{1+S}\beta \tag{4.6}$$

if the quantity

$$\beta = H_{ab} - S\cdot E(\mathrm{H}) \tag{4.7}$$

is regarded in *Mulliken*'s sense[3] as the *reduced* resonance integral, while H_{ab} is often referred to simply as the resonance integral[20].

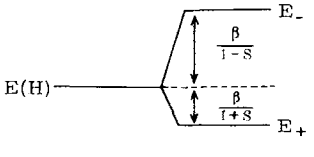
An analogous argument for the antibonding state of H_2^+

$$\psi_- = \frac{1}{\sqrt{2(1-S)}}[a-b] \tag{4.8}$$

gives the following expression for its change in energy due to interference

$$\Delta E_- = -\frac{1}{1-S}\beta \tag{4.9}$$

The fact that both positive and negative interference are possible thus leads to splitting of the energy in accordance with the well-known scheme:



Because of the denominators $(1+S)$ and $(1-S)$, the splitting is not symmetrical in this approximation. The splitting would be symmetrical about $E(\mathrm{H})$ if, as is often done in the textbooks, the overlap integral S were disregarded in relation to 1. If one considers that S has a value of ≈ 0.6 at the equilibrium distance of H_2^+ ($R = 2\ a_0$), one is inclined to think that it is not permissible to neglect S here, since in this case

$$\frac{1}{1+S} \approx 4\cdot\frac{1}{1-S} \tag{4.10}$$

It would be even more objectionable to neglect S in eq. (4.7)[15], since (again for $R = 2\ a_0$)

$$\begin{aligned}&H_{ab} \approx -0.38;\ S\cdot E(\mathrm{H}) \approx -0.3\\ &\beta \approx -0.08\end{aligned} \tag{4.11}$$

If one considers the exact energies of the bonding and of the antibonding states of H_2^+ for $R = 2\ a_0$, one obtains

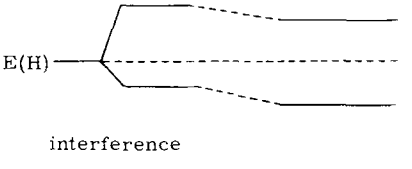
$$\begin{aligned}\Delta E_- &= +0.332\\ \Delta E_+ &= -0.102\end{aligned} \tag{4.12}$$

which is actually a non-symmetrical splitting. The quotient

$$|\Delta E_+|/|\Delta E_-|$$

however, is smaller than that obtained if only the interference is taken into account.

This is understandable, since the variation of η, which gives a different optimum for ψ_+ and ψ_-, decreases both energies. In many cases (but not for H_2^+) this decrease is such that the overall result is an almost symmetrical splitting, and that it seems as if S could be simply omitted in (4.6) and (4.9), as indicated in the following scheme.



When this is so, the energies of the bonding and of the antibonding states for a two-center one-electron bond can be approximately expressed in terms of the reduced resonance integral β by the simple relation

$$E_\pm = E(\mathrm{H}) \pm \beta \tag{4.13}$$

One can also go a step further and consider that to a first approximation only the change in the kinetic energy as a result of the interference contributes to β, the potential energy being completely disregarded. If the change in the kinetic energy is described, as in *Hellmann*'s model, by a change in the space available to the electrons, one obtains the simplest possible (and naturally also the crudest) model

of the chemical bond, the "free electron" model. If we describe the space available to the electrons of an atom by a cubic box of edge length l, the ground state of this particle in the box is given by[21]

$$E_1 = \frac{3h^2}{8ml^2} \tag{4.14}$$

The formation of a molecule is now pictured as the fitting together of two cubic boxes with one face in common and removal of the separating wall. The ground state in this brick-shaped box has the energy

$$E_2 = \frac{2h^2}{8ml^2} + \frac{h^2}{32ml^2} \tag{4.15}$$

The binding energy (decrease in energy) would thus be

$$\Delta E = E_2 - E_1 = -\frac{3h^2}{32ml^2} \tag{4.16}$$

It is somewhat more realistic, instead of allowing twice as much space for the molecule as for the atom, to assume some interpenetration of the two cubes. Let us consider the following as an explanation of the model.

To describe the H_2^+ ion, we choose l such that E_1 according to (4.14) is equal to the kinetic energy $\frac{1}{2}$ a.u. of the H atom. A simple argument then shows, since 1 a.u. $= me^4/\hbar^2$, $h = 2\pi\hbar$, and 1 $a_0 = \hbar^2/me^2$, that

$$l = \pi\sqrt{3}a_0 \approx 5a_0 \tag{4.17}$$

In H_2^+, the equilibrium distance between the nuclei is 2 a_0, so that one should expect a box length of 7 $a_0 \approx \frac{7}{5}l$ (2.5 a_0 to the right and to the left of the nuclei and 2 a_0 between the nuclei) in the direction of the axis of the molecule. The change in energy due to the increase in the size of the box is then

$$\Delta E \approx \frac{h^2}{8ml^2}\left[\left(\frac{5}{7}\right)^2 - 1\right] \approx -\frac{h^2}{16ml^2} \approx -\frac{1}{6}E_1 \approx -0.08 \text{ a.u.} \tag{4.18}$$

The binding energy estimated in this way is evidently of the correct order of magnitude. However, far-reaching conclusions should not be drawn from oversimplified models. The true electron distribution is naturally very different from that of our model. Moreover, the model can be valid only for energy *differences* (as a result of the interference), but not for the energy of the atom or molecule itself. The potential energy is completely disregarded in this model; though it has little effect on molecule formation, it is very important to the stability *e.g.* of the H atom. In the model, $\langle T \rangle$ for the H atom is $+0.5$ a.u., and $\langle V \rangle = 0$, so that $E = +0.5$ instead of the true value of -0.5 a.u.

Note that the model just discussed is semiempirical. By this we mean that it involves a quantity (in this case l) whose value is found not from the model itself but by comparison with accurate values (known from experiment or from accurate calculations; comparison in this case with the kinetic energy of the H atom in the ground state). The equilibrium distance of H_2^+[22] also was not calculated but assumed.

5. One-Electron and Many-Electron Contributions to the Chemical Bond

Let us forget for the moment the excessively simplified models and try to apply what we have learnt from H_2^+ to the bond in an arbitrarily chosen molecule. At least one point remains to be clarified before we can do this. H_2^+ contains only one electron, whereas all other molecules have more than one; in addition to the energy contributions discussed so far, therefore, there will also be contributions due to the interaction of the electrons, *i.e.*

a) contributions due to the Coulomb repulsion of the charge clouds assigned to the various electrons;

b) the so-called exchange interaction of the electrons, which is connected with the fact that the wave function of a many-electron system must be antisymmetric with respect to the interchange of two electrons (as required by the Pauli principle);

c) the so-called electron correlation, which denotes those corrections that arise from the fact that electrons are not simply charge clouds interacting as such in a static manner but that thay "try to avoid each other".

The questions we must ask ourselves are:

1. Does the presence of the electron interaction contributions fundamentally change the picture of the chemical bond that we have built up?

2. Which of the three electron interaction contributions a) to c) are important and which are not?

In this connection, one may also ask the more particular but by no means unimportant question whether an electron-pair bond (as in H_2) is fundamentally different from a one-electron bond (as in H_2^+).

Those familiar with the history of quantum chemistry will know that the first work on the theory of the chemical bond, *i.e.* that of *Heitler* and *London* on the H_2 molecule[1], was deliberately accepted as a two-electron theory. The chemical bond was correlated by *Heitler* and *London* with a so-called *exchange integral*, which has since then played a central part in the "valence bond" approximation (which is an extension of the Heitler-London model to larger molecules). However, we have known at least since the fundamental publication of *Mulliken*[3] on the MO theory that the Heitler-London exchange integral is not an exchange integral in the true sense[23], and that in fact the electron exchange between atomic orbitals is of practically no importance to chemical bonding.

The Heitler-London exchange integral is a sum of several contributions, the most important of these being essentially equal to the energy contribution due to interference in the case of H_2^+, *i.e.* it is a one-electron integral. The fact that chemical bonding was regarded for a long time as a two-electron effect (as an exchange interaction) goes back on the one hand to the tradition of assigning electron *pairs* to valence lines, and is due on the other hand to the success of the Slater theory of the atom, in which it was in fact possible to attribute the energy differences between different terms having the same configuration to exchange integrals.

The fact that *true* exchange integrals between atomic orbitals do not play a decisive part in chemical bonding is

connected with an observation made by *Mulliken*, according to which these exchange integrals can, to a close approximation, be expressed in terms of Coulomb integrals[24] and overlap integrals. As a result of the validity of this Mulliken approximation, the interference of the AOs has very little influence on the interaction of the electrons, in other words the interaction of the electrons can be calculated on a quasi-classical basis. The effect of the interference is essentially confined to the kinetic energy and to a small extent to the potential energy of the electrons in the field of the nuclei and the core electrons. These are both one-electron contributions.

In any molecule, therefore, the effects responsible for the chemical bond are the same as in H_2^+, *i.e.*:

1. Quasi-classical Coulomb interaction between nuclei and electrons of the separate (different) atoms.

2. Interference of the AOs and the associated decrease in the kinetic energy.

3. Promotion of the AOs.

Unlike the situation in H_2^+, however, it should be noted that in addition to the charge displacement from the atoms into the bonding region as a result of the interference, there is also a charge transfer from one atom to the other in the general case as a result of the difference in the electronegativities of the atoms. This charge transfer is particularly pronounced in polar (ionic) molecules. That it does contribute to bonding and the extent to which it contributes are sufficiently evident, and we shall not pursue this question further[25]. A charge transfer of this type naturally alters the quasi-classical interaction. As a fourth effect that contributes to bonding, we now merely mention:

4. Charge transfer.

When we say that the exchange interaction of the electrons is not important, we must point out that in addition to this and the Coulomb interaction of the electrons, the electron correlation mentioned earlier occurs as a third interaction. This cannot be disregarded for the occurrence of a chemical bond, and is indeed essential for a quantitative theory of the chemical bond. It is sufficient to say here that in the case of a two-electron bond it is most favorable from the standpoint of interference if the two electrons occupy the same bonding molecular orbital, but this double occupation means that the electrons come very close together, even with large distances between the nuclei. From the standpoint of electron correlation, on the other hand, it is energetically more favorable if the electrons can avoid each other. Interference and correlation therefore compete with each other in such a way that the interference predominates at short internuclear distances and the correlation at large distances. However, this competition has the overall result that the bond energy of an electron-pair bond is less than twice the bond energy of a corresponding one-electron bond (where the interference can become fully effective). The bond energy in H_2^+, for example, is 0.102 a.u.; twice this value is 0.204 a.u., whereas the bond energy in H_2 is 0.174 a.u. To complete the picture, we can now add the fifth contribution to the bond:

5. Competition between interference and correlation in electron-pair bonds.

6. Long-Range and Short-Range Forces

Whereas in the last section we distinguished between one-*electron* and many-*electron* contributions to chemical binding, we shall now classify the binding energy according to one-*center* and many-*center* contributions, "center" being identified with atom. If the Mulliken approximation is valid and if part of the electron correlation is approximately taken into account for the many-electron integrals, the energy can be expressed as follows[26]:

$$E = \sum_{\mu} E_{\mu} + \sum_{\mu<\nu} E_{\mu\nu} \tag{6.1}$$

i.e. with only one-center and two-center contributions to the bond.

The sum of the energies of the separate atoms is naturally given by

$$E^0 = \sum_{\mu} E_{\mu}^0 \tag{6.2}$$

where E_{μ}^0 is the energy of the μth atom, so that the following expression is found for the bond energy ΔE:

$$\Delta E = E - E^0 = \sum_{\mu} (E_{\mu} - E_{\mu}^0) + \sum_{\mu<\nu} E_{\mu\nu} \tag{6.3}$$

A one-center contribution $E_{\mu} - E_{\mu}^0$ to the binding energy can obviously be interpreted as the "promotion energy" of the μth atom (where we also regard conversion into an ion as promotion). A two-center contribution $E_{\mu\nu}$, on the other hand, denotes the interaction between the μth and the νth atom. Every two-center contribution of this type consists of two components, one due to the quasi-classical Coulomb interaction between the two atoms and one due to the interference of the AOs of the atoms.

$$E_{\mu\nu} = E_{\mu\nu}^{QK} + E_{\mu\nu}^{interf.} \tag{6.4}$$

There are characteristic differences between the two contributions, particularly in their range. For large distances between the μth and νth atoms, $E_{\mu\nu}^{QK}$, as is always the case for Coulomb interactions, behaves as follows:

$$\lim_{R_{\mu\nu}\to\infty} E_{\mu\nu}^{QK} = \frac{e^2 Q_{\mu} Q_{\nu}}{R_{\mu\nu}} \tag{6.5}$$

where Q_{μ} and Q_{ν} are the "effective charges" of the μth and νth atoms. This interaction has a long range, provided that Q_{μ} and Q_{ν} do not vanish. The interference contribution $E_{\mu\nu}^{interf.}$, on the other hand, is directly related to the overlap of the AOs of the two atoms. On the whole this overlap depends *exponentially* on the distance $R_{\mu\nu}$ between the atoms ab, *i.e.* it has a short range and is important only between atoms that are *nearest neighbors* in the molecule. $E_{\mu\nu}^{QK}$, on the other hand, also acts between atoms that are further apart in the molecule, provided that these carry effective charges.

It is also interesting to note that the interference contributions contain essentially only one-electron contributions of the type discussed for H_2^+.

Let us consider in particular a molecule with nonpolar (or only weakly polar) bonds in which all the effective charges Q_μ of the atoms are negligible. The only contributions to the chemical bond are then short-range contributions, *i. e.* contributions that act only between nearest neighbors. The bond energy then depends only on the nearest neighbors of any given atom and not on the actual geometry of the molecule. The proximity conditions are referred to collectively as the *topology* of the molecule (one could also speak of local geometry as opposed to overall geometry). As an example, let us consider *cis*- and *trans*-1,3-butadiene, both of which have the same topology but different geometry.

Since Q_μ is in fact approximately 0 for all μ, long-range forces are of no decisive importance and the energy difference between the two "isomers" is extremely small.

The description of the bonding in molecules without polar bonds is greatly facilitated by the fact that to a first approximation, this description involves only the topology and not the geometry of the molecule. It should be remembered, however, that a description that is permissible for nonpolar molecules may be completely wrong for polar molecules. A number of inconsistencies in the use of greatly simplified quantum-chemical methods are due to the fact that these methods were applied to polar molecules though they are justified only for nonpolar ones.

7. MO Theory

The term MO theory is unfortunately used with two meanings, which, though connected, mean fundamentally different things. We are referring to the distinction between the "complete MO theory" and the "one-electron MO theory".

In the complete MO theory, one begins with a wave function that is an antisymmetrized product of molecular orbitals (MOs), and the best MOs are then determined such that the total energy becomes a minimum. The electron correlation is ignored here, and errors also arise because of the necessarily finite basis of the AOs (from which the MOs are constructed as linear combinations). Otherwise, however, none of the integrals or other terms in the energy expression are disregarded or approximated.

The one-electron MO theory, on the other hand, which we shall now describe briefly, is the result of a series of simplifications of the quantum-chemical energy expression and omissions of contributions that are regarded as small.

In a molecule in which the effective charges Q_μ of all the atoms vanish (this is a more rigorous requirement than that the molecule should be nonpolar, but we shall use the simple description "nonpolar"), there are no long-range forces, *i. e.* no direct interactions between non-adjacent atoms. Thus only contributions for nearest neighbors, *i. e.* for atoms connected directly by chemical bonds, need be taken into account in the sum $\sum_{\mu<\nu} E_{\mu\nu}$. These contributions are closely connected with the interference of the AOs[27], and the following expression is approximately valid

$$E_{\mu\nu} = \sum_i n_i c_\mu^i c_\nu^i H_{\mu\nu} \tag{7.1}$$

the sum being taken over the MOs. In this expression, n_i is the occupation number of the i-th MO (n_i may have the values 0, 1, or 2), and c_μ^i is the coefficient of the μth AO in the i-th MO. Thus if ψ_i is the i-th MO and λ_μ is the μth AO, ψ_i can be written as

$$\psi_i = \sum_\mu c_\mu^i \chi_\mu \tag{7.2}$$

Finally, $H_{\mu\nu}$ in (7.1) for $\mu \neq \nu$ is the resonance integral[20] between the μth and the νth AOs, and is directly connected with the interference of this MO, whereas $H_{\mu\mu}$ can be interpreted under certain conditions as the ionization potential of the μth AO in its valence state.

We assumed in eq. (7.1) that each atom has only one AO available; it would otherwise have been necessary to give the AOs two subscripts, one denoting the atom and the other the AO of an atom, and it would also be necessary in (7.1) to carry out summation over the AOs of the μth and of the νth atoms. For clarity, we limit ourselves to a single subscript (corresponding to the case of one AO per atom).

If (7.1) is a sufficiently good approximation, the MO coefficients c_μ^i can be calculated from a system of linear equations of the following type[28]

$$\sum_\nu H_{\mu\nu} c_\nu^i = \varepsilon_i \sum_\nu S_{\mu\nu} c_\nu^i \tag{7.3}$$

where

$$S_{\mu\nu} = \int \chi_\mu \chi_\nu \, d\tau \tag{7.4}$$

is the overlap integral of the AOs χ_μ and χ_ν.

The system of equations (7.3) can be solved only if the (for the time being unknown) ε_i assume certain numerical values, *i. e.* values such that the determinant

$$|H_{\mu\nu} - \varepsilon_i S_{\mu\nu}| \tag{7.5}$$

vanishes. The ε_i can be interpreted as the energies of the MOs, and the binding energy is approximately given by

$$\Delta E = \sum_i n_i \varepsilon_i - \sum_\mu n_\mu H_{\mu\mu} \tag{7.6}$$

In this equation, n_μ of course denotes the occupation number of the AO in the isolated atom.

Under certain conditions, it is justifiable to equate the overlap integral $S_{\mu\nu}$ for $\mu \neq \nu$ to zero and *at the same*

time to replace the resonance integrals $H_{\mu\nu}$ by the reduced resonance integrals $\beta_{\mu\nu}$[15].

If the diagonal elements $H_{\mu\mu}$ are then denoted by α_μ and if the Hückel matrix is defined by the elements $\tilde{H}_{\mu\nu}$

$$\tilde{H}_{\mu\nu} = \begin{cases} \alpha_\mu \text{ for } \mu = \nu \\ \beta_{\mu\nu} \text{ for } \mu \neq \nu \end{cases} \tag{7.7}$$

then from (7.3) and (7.5)

$$\sum \tilde{H}_{\mu\nu} c_\nu^i = \varepsilon_i c_\mu^i \tag{7.8}$$

$$|\tilde{H}_{\mu\nu} - \varepsilon_i \delta_{\mu\nu}| = 0 \tag{7.9}$$

whereas (7.6) remains formally the same. The energy ε_i assigned to the i-th molecular orbital is then simply equal to the i-th eigenvalue of the Hückel matrix. The lowest value of ΔE according to (7.6), *i.e.* the binding energy of the molecule, is obtained if the lowest MOs are filled in sequence. According to the Pauli principle, the maximum occupation number is $n_i = 2$. An MO φ_i, which is a linear combination of the AOs in this approximation, gives binding between two atomic orbitals χ_μ and χ_ν only if the interference between these atoms is positive, *i.e.* if the coefficients c_μ^i and c_ν^i (cf. (7.2)) have the same sign (provided $S_{\mu\nu} > 0$), in other words if

$$c_\mu^i \cdot c_\nu^i > 0 \tag{7.10}$$

Otherwise, *i.e.* if $c_\mu^i c_\nu^i$ is negative, negative interference exists between χ_μ and χ_ν, and we have the opposite of binding. The sum over the contributions of all MOs[29]

$$p_{\mu\nu} = \sum_i n_i c_\mu^i c_\nu^i \tag{7.11}$$

is consequently a measure of the strength of the bond between these atoms, and is therefore known as the bond order[29]. It must be emphasized, however, that bond orders can be defined only within certain approximations, and are not quantities that have anything to do with the bond itself.

Negative interference means a nodal surface[30] of the MOs between the AOs in question. The (energetically) lowest MOs have no nodes between the atoms, and the number of nodes generally increases with increasing ε_i. The same result is also found when one attempts to describe the bonding by means of the electron gas model instead of by the Hückel MO approximation, as indeed a close analogy exists between the HMO approximation and the free electron model[31].

Let us consider a number of examples to illustrate the arguments of this section.

1. *H_2^+ and H_2.* Both have the Hückel matrix

$$\tilde{H} = \begin{pmatrix} \alpha & \beta \\ \beta & \alpha \end{pmatrix}$$

with the eigenvalues

$$\varepsilon_1 = \alpha + \beta$$

$$\varepsilon_2 = \alpha - \beta$$

Since $\beta < 0$, ε_1 is the lower of the two MO energies. The occupation numbers are $n_1 = 1$ for H_2^+ and $n_1 = 2$ for H_2, and the bond energies are therefore

$$\Delta E = (\alpha + \beta) - \alpha = \beta \text{ for } H_2^+$$

$$\Delta E = 2(\alpha + \beta) - 2\alpha = 2\beta \text{ for } H_2$$

We have already derived this approximate expression for H_2^+ in Section 4 and we also explained the approximations that lead to this result. The one-electron MO approximation gives exactly twice the bond energy of a one-electron bond for a two-electron bond. It was shown in Section 4 that this is not quite correct, the exact values being

$$\Delta E = -0.102 \text{ a.u. for } H_2^+$$

$$\Delta E = -0.174 \text{ a.u. for } H_2$$

2. *He_2.* The Hückel matrix and the eigenvalues are the same as for H_2. However, it is now necessary to accommodate four electrons; this is possible only if both ψ_1 (which is bonding) and ψ_2 (which is antibonding) are doubly occupied. With $n_1 = n_2 = 2$ one obtains

$$\Delta E = 2(\alpha + \beta) + 2(\alpha - \beta) - 4\alpha = 0$$

Thus no bonding occurs between two He atoms[32], and similarly the electrons of the K shells in the molecules Li_2 to F_2 take practically no part in bonding. The fact that there is no chemically bound Ne_2 molecule can be explained in a similar manner.

3. *H_3^+.* At equilibrium, this molecule has the structure of an equilateral triangle. Each of the three atoms is directly bound to each of the others, so that the Hückel matrix is

$$\tilde{H} = \begin{pmatrix} \alpha & \beta & \beta \\ \beta & \alpha & \beta \\ \beta & \beta & \alpha \end{pmatrix}$$

The eigenvalues ε_i of this matrix are

$$\varepsilon_1 = \alpha + 2\beta$$

$$\varepsilon_2 = \alpha - \beta$$

$$\varepsilon_3 = \alpha - \beta$$

There is room for two electrons in the lowest MO, $n_1 = 2$.

$$\Delta E = 2(\alpha + 2\beta) - 2\alpha = 4\beta$$

The binding energy of H_3^+, with respect to $2H + H^+$, should therefore be twice that of H_2, with respect to 2 H, *i.e.* the proton affinity of H_2 should be roughly equal to the binding energy of H_2. This agrees surprisingly well with experimental values and with values from good quantum-chemical calculations.

H_3^+ embodies the simplest case of a three-center bond. This good functioning of the Hückel approximation for H_3^+ should not be overprized since the Hückel approxima-

tion completely fails for the neutral H_3. With $n_1=2$ and $n_2=1$, we should have

$$\Delta E = 2(\alpha+2) + \alpha - \beta - 3\alpha = 3\beta$$

i.e. H_3 should have a binding energy of β with respect to H_2+H, whereas in reality H_3 is not a stable molecule[33].

4. *BeH_2 (linear).* The Hückel matrix here is

$$\tilde{H} = \begin{pmatrix} \alpha_K & 0 & 0 & 0 & 0 \\ 0 & \alpha_s & 0 & \beta_{sh} & \beta_{sh} \\ 0 & 0 & \alpha_p & \beta_{ph} & -\beta_{ph} \\ 0 & \beta_{sh} & \beta_{ph} & \alpha_h & 0 \\ 0 & \beta_{sh} & -\beta_{ph} & 0 & \alpha_h \end{pmatrix}$$

The first line (column) relates to the 1s AO (K) of Be, the second line (column) to the 2s AO of Be, the third to the 2p AO of Be, and the fourth and fifth to the two H atoms. The reduced resonance integral β_{sh} takes into account the interference between 2s of the Be atom and 1s of an H atom.

Since the 1s AO of Be is so strongly localized in the neighborhood of the nucleus that it does not interfere with the 1s AOs of the H atom, we find that it is an MO by itself.

$$\Psi_1 = K$$

Since the molecule is symmetrical with respect to inversion at the Be atom, the MOs must be either symmetrical or antisymmetrical with respect to this center. For each type there is one bonding and one antibonding MO. Since we have to accommodate six electrons, we need the two bonding MOs

$$\psi_2 = c_{22}s + c_{24}(h_1 + h_2)$$
$$\psi_3 = c_{33}p + c_{34}(h_1 - h_2)$$

in addition to ψ_1. In ψ_2 the 2s AO of the Be atom binds the H atoms, and in ψ_3 the 2pσ AO; both are three-center MOs.

The molecular orbitals of the MO theory are found to be delocalized over the entire molecule, even though such delocalization contradicts chemical intuition. One might have preferred to see BeH_2 described by two-center Be—H bonds.

8. Localized and Delocalized Bonds

A fully equivalent localized description is in fact possible for molecules like BeH_2. To understand this, one must bear in mind that the MOs are not uniquely defined, and that a different choice of MOs can give the same results with respect to all the observable properties of a molecule.

The wave function of the MO theory (but we must base our argument here on the "complete MO theory" and not on the "one-electron MO theory") is a Slater determinant.

To illustrate this let us consider a very simple example, *i.e.* the first excited triplet state of the H_2 molecule, in which both the bonding and the antibonding MO are singly occupied with equal spin[34].

The wave function (spin-free) in the determinant form is

$$\phi = \frac{1}{\sqrt{2}} \begin{vmatrix} \psi_+(1) & \psi_+(2) \\ \psi_-(1) & \psi_-(2) \end{vmatrix} \tag{8.1}$$

or multiplied out

$$\phi = \frac{1}{\sqrt{2}} \{\psi_+(1)\psi_-(2) - \psi_-(1)\psi_+(2)\} \tag{8.2}$$

We shall now assume further that the interatomic distance is so great that the overlap between the AOs a and b becomes vanishingly small, so that

$$\psi_\pm = \frac{1}{\sqrt{2}}[a \pm b] \tag{8.3}$$

Insertion of (8.3) in (8.2) leads, after simple multiplication, to

$$\phi = \frac{1}{\sqrt{2}} \{a(1)\,b(2) - b(1)\,a(2)\} = \frac{1}{\sqrt{2}} \begin{vmatrix} a(1) & a(2) \\ b(1) & b(2) \end{vmatrix} \tag{8.4}$$

The wave function ϕ thus does not change when the delocalized MOs ψ_+ and ψ_- are replaced by the localized MOs a and b. This is possibly not too surprising in the example chosen. If both the bonding (ψ_+) and the antibonding (ψ_-) linear combinations of the AOs a and b are occupied, no bonding occurs and the electrons can also be packed, intuitively speaking, into the original AOs. It is clear that in the ground state of H_2 with the one-determinant wave function in which ψ_+ is doubly occupied (with α and β spin), a different choice of the MOs is not possible, since only one MO occurs in the wave function.

In the ground state of He_2, on the other hand, we have substantially the same situation as in the H_2 triplet. Instead of double occupation of each of the two MOs ψ_+ and ψ_-, the AOs a and b may each be doubly occupied. There is no molecule He_2, but only two He atoms.

Let us return to the example of the H_2 triplet. The AOs a and b are obtained from the MOs ψ_+ and ψ_- in accordance with (the converse of (8.3))

$$a = \frac{1}{\sqrt{2}}[\psi_+ + \psi_-]$$
$$b = \frac{1}{\sqrt{2}}[\psi_+ - \psi_-] \tag{8.5}$$

One can also satisfy oneself that any choice of orbitals φ_1 and φ_2 in accordance with

$$\varphi_1 = u_{11}\psi_+ + u_{12}\psi_-$$
$$\varphi_2 = u_{21}\psi_+ + u_{22}\psi_- \tag{8.6}$$

leads to the exactly identical wave functions

$$\phi = \frac{1}{\sqrt{2}} \begin{vmatrix} \psi_+(1) & \psi_+(2) \\ \psi_-(1) & \psi_-(2) \end{vmatrix} = \frac{1}{\sqrt{2}} \begin{vmatrix} \varphi_1(1) & \varphi_1(2) \\ \varphi_2(2) & \varphi_2(2) \end{vmatrix} \tag{8.7}$$

provided that the matrix of the coefficient is unitary, *i.e.* provided that (for real u_{ik})

$$\begin{aligned} (u_{11})^2 + (u_{12}{}^2 = (u_{21})^2 + (u_{22})^2 = 1 \\ u_{11}\,u_{21} + u_{12}\,u_{22} = 0 \end{aligned} \tag{8.8}$$

Among the infinite range of possible choices for the two MOs, there are two outstanding sets (and this is generally valid, not only for our example), *i.e.*:

1. The canonical MOs, in this case ψ_+ and ψ_-; these are adapted to the symmetry of the problem, ψ_+ being symmetric with respect to inversion at the symmetry center of the molecule, and ψ_- antisymmetric.

2. The equivalent MOs[35], in this case *a* and *b*; these are interchanged on application of symmetry operators (in this case inversion at the center).

In the example considered, the equivalent MOs happen to be identical with atomic orbitals (AOs).

This is not the case *e.g.* in BeH_2, were the equivalent MOs

$$\varphi_1 = \frac{1}{\sqrt{2}}(\psi_2 + \psi_3) = \frac{c_{22}}{\sqrt{2}}s + \frac{c_{33}}{\sqrt{2}}p + \frac{(c_{24} + c_{34})}{\sqrt{2}}h_1 + \frac{(c_{24} - c_{34})}{\sqrt{2}}h_2$$

$$\varphi_2 = \frac{1}{\sqrt{2}}(\psi_2 - \psi_3) = \frac{c_{22}}{\sqrt{2}}s - \frac{c_{33}}{\sqrt{2}}p + \frac{(c_{24} - c_{34})}{\sqrt{2}}h_1 + \frac{(c_{24} + c_{34})}{\sqrt{2}}h_2 \tag{8.9}$$

can be constructed from the MOs φ_2 and φ_3 (cf. Section 7).

Since, as it turns out,

$$c_{22} \approx c_{33}; \quad c_{24} \approx c_{34} \tag{8.10}$$

we have approximately

$$\begin{aligned} \varphi_1 &\approx c_{22}\frac{s+p}{\sqrt{2}} + \sqrt{2}\cdot c_{24}\cdot h_1 \\ \varphi_2 &\approx c_{22}\frac{s-p}{\sqrt{2}} + \sqrt{2}\cdot c_{24}\cdot h_2 \end{aligned} \tag{8.11}$$

i.e. the equivalent MOs are approximately localized in one Be—H bond each, and can be approximately interpreted as two-center MOs, each formed from the AO of a hydrogen atom and a "hybrid AO" of the central atom

$$\begin{aligned} d_1 &= \frac{1}{\sqrt{2}}(s+p) \\ d_2 &= \frac{1}{\sqrt{2}}(s-p) \end{aligned} \tag{8.12}$$

Localized bonds in the chemical sense are in fact always present if it is possible to construct equivalent MOs that, to a good approximation, are each localized in one bond. However, such a transformation is not always possible and *Hund*[36] was able in 1931 to state the necessary condition for the possibility of the localization of bonds. This condition, for each atom in the molecule, is:

number of valence electrons = number of AOs participating in the bond = number of neighbors

The condition is satisfied in BeH_2. Be has 2 valence electrons (the 1s electrons, which do not take part in bonding, are not counted), 2 neighbors, and 2 AOs (2s and 2p) that participate in bonding. The corresponding number for each of the two H atoms is 1.

In BeH_2^+, however, localization is no longer possible, since there is only one valence electron of Be available, whereas the number of AOs and the number of neighbors remain the same. This is an indication that the use of localized MOs is unsuitable for the description of the ionization of molecules (which is now so important in connection with photoelectron spectroscopy), since such MOs are meaningful for neutral molecules, but not for ionized molecules.

As can be generally shown, the orbitals whose energies represent the best one-electron approximation for ionization potentials are in fact the canonical MOs. The orbitals that the photoelectron spectroscopist must think about are necessarily the canonical orbitals. It would be quite wrong, however, to conclude from the delocalization of the ionization that the description of neutral molecules in the ground state by localized bonds is invalid. This error is unfortunately often made[37].

H_3^+, for example, cannot be described by localized two-center bonds. In this case each H has $\frac{2}{3}$ electron, 2 neighbors, and 1 valence AO.

The π bond in benzene is not localized either, *i.e.* not localizable. In this case (now only with reference to the π bond) the number of neighbors is 2, whereas the number of electrons and of AOs is only 1. A similar situation is found for diborane B_2H_6, in which each B atom has 4 H atoms as neighbors but only 3 valence electrons. However, B_2H_6 can be described by four 2-center BH and two 3-center BHB bonds. The bonds are thus largely localized even in B_2H_6, but in localized 2-center and 3-center bonds. This localizability of the bonds completely collapses in other boron hydrides, *e.g.* in $[B_{12}H_{12}]^{2-}$, where only the canonical (symmetry-adapted) MOs are adequate (as in benzene).

Systems with delocalized bonds (many-center bonds) are often characterized by unusual stability, particularly when the number of valence electrons is smaller than the number that would correspond to localized electron-pair bonds (electron-deficient compounds). This is not surprising, since it can be seen even from the example of H_2/H_3^+ that two electrons form a two-center bond with a binding energy of $\Delta E \approx -100$ kcal/mol, whereas the same two electrons form a three-center bond with $\Delta E \approx -200$ kcal/mol.

9. Electron Correlation and the Chemical Bond

In the use of a one-electron MO theory (such as the Hückel approximation), the quasi-classical electrostatic interaction of the effective charges in the molecule is disregarded, among other things. A complete MO theory takes these long-range forces into account, but even this is still far from an exact solution of the quantum-mechanical problem. As was mentioned, the errors of the one-determinant approximation are referred to as electron correlation.

Electron correlation has an impact on the chemical bond in several respects. Two effects in particular are important. The first is concerned with the false asymptotic behavior of the MO wave function for large internuclear distances. It has already been mentioned that in the MO theory two electrons occupy the same orbital. This means that they come very close together, even at large internuclear distances.

By taking electron correlation into account, one gives the electrons the opportunity to avoid each other, so to speak. One can readily understand that this contribution of electron correlation increases with the internuclear distance. In the H_2 molecule, for example, it is to be expected for large R that there will be one electron in the neighborhood of each nucleus, whereas the wave function of the MO approximation forces the electrons to be situated in the neighborhood of the same nucleus with the same probability as in the neighborhood of different nuclei. It is often said (though this formulation is somewhat misleading) that the MO function gives too much weight to "ionic structures" at large distances. The correlation under discussion here, which ensures the correct behavior for $R \rightarrow \infty$, is known as left-right correlation. It allows the electrons to avoid each other by ensuring that when one electron is on the left (at nucleus A) the other is preferentially on the right (at nucleus B). There are also in-out and angular correlations, which must be taken into account if binding energies are to be calculated accurately.

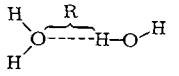
All the correlation effects just mentioned refer to a single bond electron pair, and one can therefore speak of intra-bond correlation. Its contribution is important whenever unpaired electrons participate in a bond, as can be seen from the following list[38,39].

	ΔE (MO) [eV]	$\Delta E_{corr.}$ [eV]
H_2	−3.64	−1.11
Li_2	−0.17	−0.88
N_2	−5.27	−4.63
F_2	+1.37	−3.05

As is generally believed, the correlation energy does not change much if no electron pairs are separated on dissociation of the molecule, the number of electron pairs remaining the same, *e.g.* in semipolar bonds such as

$$NH_4^+ \rightarrow NH_3 + H^+$$

or in hydrogen bonds



However, constancy of the number of electron pairs is not enough to ensure approximate constancy of the correlation energy on dissociation. In addition to the *intra*-bond correlation, the correlation between different bonds, which may be regarded as a sort of van der Waals attraction between these bonds, is also found to be important. Undoubtedly a rather spectacular case in which the change in the *inter*-bond correlation energy makes a decisive contribution to the binding energy is the system $2\,BH_3 \rightarrow B_2H_6$. The MO theory gives a value of approximately 10 kcal/mol for the dimerization energy of BH_3, while the change in the inter-bond correlation energy is approximately 25 kcal/mol, corresponding to a total dimerization energy of about 35 kcal/mol[40]. In BH_3, there are only three possible pairs of bonds with a common B atom whereas in B_2H_6 there are eleven such pairs, *i.e.* five more than in two separate BH_3 units. The change in the correlation energy that accompanies the change in the number of adjacent bonds is responsible for the bulk of the "electron-deficient bonding" in B_2H_6[40]. This should be born in mind particularly since chemistry textbooks are never at a loss to explain this type of bonding with the aid of a qualitative MO theory without even considering electron correlation.

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[1] Based on a lecture given in Vienna on May 18, 1972, on the occasion of the 75th anniversary of the Verein Österreichischer Chemiker. This article may also be regarded as Part II of the series "Methods and Applications of Quantum Chemistry" (Part I: Physical and Mathematical Basis. *W. Kutzelnigg*, Angew. Chem. 78, 789 (1966); Angew. Chem. internat. Edit. 5, 823 (1966)). Knowledge of Part I is not essential for Part II.

[2] *W. Heitler* and *F. London*, Z. Phys. 44, 455 (1927).

[3] *R. S. Mulliken*, J. Chim. Phys. 46, 497, 675 (1949). The text originally written by *Mulliken* in English has been published here in a French translation. A mimeographed version of the original manuscript used to be available.

[4] *K. Ruedenberg*, Rev. Mod. Phys. 34, 326 (1962).

[5] The integration, which is conveniently carried out in spherical polar coordinates, leads for ψ according to (2.8), of which that according to (2.7) is a special case (with $\eta = 1$), to $\int \psi^2 d\tau = N^2 \cdot \pi \cdot \eta^{-3} = 1$, whence it follows directly:

$$N = \sqrt{\frac{\eta^3}{\pi}}.$$

[6] The mean $\langle f(x) \rangle$ of any function $f(x)$ averaged over the distribution $\rho(x)$ is defined as

$$\langle f(x) \rangle = \int_{-\infty}^{\infty} \rho(x) f(x) d\tau$$

This integral vanishes for $f(x) = x$, since replacement of x by $-x$ leaves $\rho(x)$ unchanged but reverses the sign of $f(x)$. To each contribution in the integral for positive x, there is an exactly opposite contribution for negative x, so that the integral as a whole vanishes.

[7] The uncertainty of the mean of a function $f(x)$ is defined as

$$\Delta f(x) = + \{\langle f^2(x) \rangle - \langle f(x) \rangle^2\}^{\frac{1}{2}} = + \{\int \rho f^2 d\tau - (\int \rho f d\tau)^2\}^{\frac{1}{2}}$$

Since $\langle f(x)\rangle$ vanishes in the given case $[f(x)=x]$, we have simply

$$\Delta x = + \{\rho x^2 d\tau\}^{\frac{1}{2}} = + \left\{\frac{1}{\eta^2}\right\}^{\frac{1}{2}} = \frac{1}{\eta}$$

in atomic units of length (a_0).

Whereas the mean of x, y, or z vanishes, that of r is different from zero. One obtains

$$\langle r\rangle = \frac{3}{2\eta}$$

The mean distance of the electron from the nucleus, apart from a factor of 1.5, is thus equal to the uncertainty of the x coordinate (for $y=z=0$).

[8] If the wave function $\psi(x)$ of a quantum-mechanical state is given, the probability amplitude $\phi(p_x)$ for the distribution of the corresponding momentum component p_x is generally given by

$$\phi(p_x) = (2\pi)^{-\frac{1}{2}} \int_{-\infty}^{+\infty} \exp\left(\frac{i p_x x}{\hbar}\right) \cdot \psi(x) dx$$

i.e. by a Fourier transformation. The probability that a particle has a momentum between p_x and $p_x + dp_x$ is then simply $|\phi(p_x)|^2\, dp_x$. For the function (2.8) one obtains (in a three-dimensional generalization of the above argument)

$$\phi(p) = \sqrt{\frac{32}{\pi}} \cdot \frac{\eta^{\frac{5}{2}}}{(p^2+\eta^2)^2}$$

where $p = \sqrt{p_x^2+p_y^2+p^2}$ is the magnitude of the momentum, and p is measured in units of $\hbar/a_0$.

The mean momentum corresponding to our wave function (2.8) is

$$\langle p\rangle = \frac{8}{3\pi} \cdot \eta \cdot \frac{\hbar}{a_0}$$

Compare this with Δp_x according to eq. (2.1). The relation between positional distribution and momentum distribution used here is a rigorous formulation of the uncertainty relation.

[9] The reader may be surprised that we were able to derive the wave function and the energy of the ground state of the H atom without explicitly referring to the Schrödinger equation. In fact, however, the Schrödinger equation is equivalent to the variation principle

$$\delta E = \delta\{\langle T\rangle + \langle V\rangle\} = 0$$

The wave function ψ, which makes the energy stationary with respect to *arbitrary* variations of ψ, is automatically a solution of the Schrödinger equation. We have not allowed all variations of ψ here, but have varied only η; this limitation is not serious because the exact wave function is contained in the family of "variation functions" (*i.e.* for $\eta=1$). If we had chosen *e.g.* the expression $\psi = N \cdot e^{-\alpha r^2}$ instead of (2.8) and tried to find the minimum of E as a function of α, we would have obtained only an approximate solution of the Schrödinger equation. However, we could have been confident that the energy calculated in this way would be *higher* than the true energy; the more closely our ψ approaches the correct ψ, the nearer is the calculated energy to the true energy. To understand that our procedure is really equivalent to a solution of the Schrödinger equation, one must appreciate that we have correctly calculated the expected value $\langle T\rangle$ of the kinetic energy; this can be done either in the usual manner by using the operator of the kinetic energy and the wave function in the "configurational representation" or, as we have done here, by using both in the "momentum representation", in which the momentum operator is simply multiplicative.

[10] In analogy with (3.2) we also think of the momentum distribution as being formed quasi-classically from those of the separate atoms.

[11] We use the term "quasi-classical" here in the sense introduced by *Ruedenberg* [4]. This has nothing to do with the WKB approximation, which was occasionally also described as "quasi-classical", though the description "semi-classical" is more usual.

[12] The kinetic energy of half an electron in each of the atomic orbitals a and b and the potential energy in the field of its own nucleus together give exactly the energy $E(H)$ of a H atom in the field of its nucleus. In addition to this there are the potential energy e^2/R of the internuclear repulsion and twice the attraction $-E_{Ke}$ of half an electron in an AO by the other nucleus. There is no repulsion between electrons, since there is only one electron present at all, and there is no "self-interaction" of an electron.

[13] The potential energy of the interaction of a point particle of charge q and a spherically symmetrical charge distribution ρ of total charge Q is simply $V=qQ/R$, where R is the distance of the particle from the center of gravity of the charge distribution, if the particle is outside the charge distribution. It is $V=0$ if the charge distribution ρ is situated in a spherical shell and the particle is situated in the (charge-free) interior of the spherical shell. If the particle is situated anywhere within the charge distribution, ρ can always be divided into two components such that the particle is outside with respect to one and inside with respect to the other. Only the first of these two components contributes to the potential energy.

If the nucleus B penetrates into the charge cloud of the electron in the AO, the attraction between the two is smaller in magnitude than the internuclear repulsion.

[14] *H. Hellmann*, Z. Phys. *35*, 180 (1933).

[15] The success of the calculations in which overlap is neglected is due to a misconception that was pointed out in particular by *Mulliken* [3]. The energy expression of the LCAO approximation for H_2^+ is

$$E_\pm = \frac{E(H) + E_{QK} \pm H_{ab}}{1 \pm S}$$

where H_{ab}, the so-called resonance integral, denotes the energy (kinetic + potential) belonging to the charge distribution *a.b.* If one neglects S (though in reality $S=0.6$), one obtains

$$E_\pm = E(H) + E_{QK} \pm H_{ab}$$

On the other hand, the correct $E_\pm$ can be transformed to

$$E_\pm = E(H) + E_{QK} \pm \frac{H_{ab} - S[E(H) + E_{QK}]}{1 \pm S} = E(H) + E_{QK} \pm \frac{\beta}{1 \pm S}$$

The correct expression and the incorrect expression are now formally very similar. When, as was usually the case, H_{ab} and β were not really calculated but regarded as semi-empirically adjustable parameters, it was practically impossible to differentiate between the two possibilities, and it appeared that overlap could be neglected. Neglect of overlap actually means that the bond energy is expressed by the reduced resonance integral β instead of by the resonance integral H_{ab} [3].

[16] The Hellmann-Feynman theorem says that the forces acting on a nucleus in a molecule are exactly equal to those calculated electrostatically from the given charge distribution of the electrons and the other nuclei. However, the critical point is that the Hellmann-Feynman theorem is valid only for the charge density calculated from the *exact* wave function, and not for those calculated from approximate wave functions. The Hellmann-Feynman theorem is therefore unsuitable for the theory of the chemical bond, since we are always concerned here with approximate wave functions. The charge density that is actually built up in a molecule is determined not only by the electrostatic factors but also by the kinetic energy; a purely electrostatic model of the chemical bond is therefore impossible.

[17] *E.g. P. O. Löwdin*, J. Mol. Spectrosc. *3*, 46 (1959). The reproach that *Hellmann* had not taken the virial theorem into account is the more grotesque in that in the same article in which he proposed the picture of the chemical bond that is named after him, *Hellmann* derived the virial theorem for molecules (simultaneously with and independently of *Slater*) and discussed in detail its role in connection with models of the chemical bond.

[18] *M. J. Feinberg, K. Ruedenberg*, and *E. L. Mehler*, Advan. Quantum Chem. *5*, 28 (1970); *M. J. Feinberg* and *K. Ruedenberg*, J. Chem. Phys. *54*, 1495 (1971).

[19] In reality, the deformation is rather more complicated, but the major part of this deformation is taken into account for H_2^+ by a variation of η.

[20] *Ruedenberg* [4] uses the symbol β for the original resonance integral H_{ab} (cf. [15]) and γ for the reduced resonance integral (4.7). *Mulliken* [3] uses the symbols γ and β in exactly the opposite senses.

[21] The derivation of this expression can be found in any introductory textbook of quantum mechanics. The energy of the ground state for a one-dimensional motion is $h^2/8ml^2$, and for an electron in a box having the edge lengths a, b, and c is given as $\frac{h^2}{8m}\left(\frac{1}{a^2}+\frac{1}{b^2}+\frac{1}{c^2}\right)$.

[22] This argument suggests that in a description of the chemical bond by the free electron model, the box should be so chosen that about one bond length is left over to the right and to the left of the outer atoms. The contributions of the kinetic energy normal to the bond direction can be completely eliminated in this approach, since they do not change during the development of the bond; the so-called one-dimensional free electron model thus becomes plausible.

[23] By "true" we mean the definition of the exchange integrals in the atomic theory.
The "exchange integral" of the Heitler-London theory is defined as

$$K = \int a(1)b(2)H(1,2)b(1)a(2)\mathrm{d}\tau_1\mathrm{d}\tau_2$$

where $H(1,2)$ is the complete Hamiltonian operator of the H_2 molecule. If we break down $H(1,2)$ into one-electron and two-electron contributions and introduce the abbreviations that are more familiar to us from H_2^+, we obtain for K:

$$K = 2S \cdot H_{ab} - 2S \cdot E_{K\epsilon} + S^2 \cdot \frac{e^2}{R} + (ab|ba)$$

where $(ab|ba)$ is an exchange integral in the "true" sense

$$(ab|ba) = \int a(1)\, b(2) \frac{1}{r_{12}} b(1)\, a(2)\, \mathrm{d}\tau_1\, \mathrm{d}\tau_2$$

This is positive, whereas K as a whole is negative. The dominant contribution to K is $2S \cdot H_{ab}$, and this is directly connected with the interference of the AOs (exactly as for H_2^+). H_{ab} and S are *one-electron contributions*, *i.e.* each is obtained by integration over the coordinates of one electron.

[24] The term "Coulomb integrals" denotes integrals of the form

$$\int [a(1)]^2 \frac{1}{r_{12}} [b(2)]^2\, \mathrm{d}\tau_1\, \mathrm{d}\tau_2$$

that describe the Coulomb repulsion of two electrons in the AOs a and b, which are therefore quasi-classical in nature.

[25] In the limiting case of purely ionic bonding, the binding energy consists, to a good approximation, of two contributions: one component $I_A - A_B$, the difference between the ionization energy of one atom and the electron affinity of the other, which represents the energy change due to charge transfer and is the only contribution present for $R \rightarrow \infty$, and the contribution of the Coulomb attraction of the opposite charges formed on the atoms. These two contributions naturally also play a certain part in polar but not purely ionic compounds.

[26] It is not entirely self-evident that an approximate breakdown of the energy into one-center and two-center contributions is possible, and the derivation of eq. 6.1 with explicit expressions for E_μ and $E_{\mu\nu}$ is not trivial. For details, see the book to be published by Verlag Chemie, Weinheim, *W. Kutzelnigg:* Einführung in die Theoretische Chemie, Bd. 2: Die chemische Bindung [Introduction to Theoretical Chemistry, Vol. 2: The Chemical Bond].

[27] The results for H_2^+ suggest that in nonpolar molecules the quasi-classical repulsion of the atoms becomes effective only at distances shorter than the bond length, so that its contribution is small when the geometry is close to the equilibrium geometry.

[28] The system of equations (7.3) is obtained as the condition that the optimum c_μ^i must satisfy if one tries to find the minimum of the energy expression (7.1) as a function of the coefficients c_μ^i with the subsidiary condition that the MOs (7.2) are normalized to 1 and are mutually orthogonal.

[29] *C. A. Coulson* and *H. C. Longuet-Higgins*, Proc. Roy. Soc. London *A 191*, 39 (1947).

[30] Nodal surfaces are surfaces on which the wave function vanishes in such a way that it has opposite signs on either side of the nodal surface.

[31] *K. Ruedenberg*, J. Chem. Phys. *22*, 1878 (1954); *N. S. Ham* and *K. Ruedenberg*, *ibid. 29*, 1199, 1215 (1958).

[32] The potential curve for He_2 has in fact a minimum in the ground state, this minimum occurring at a distance of 5.6 a_0 and a "binding energy" of about 20 cal/mol. The mechanism of the occurrence of this "van der Waals minimum" is fundamentally different from that of a true chemical bond, and we cannot discuss it here.

[33] The explanation for the failure of the one-electron MO theory in this fairly simple example is rather complicated (cf. the textbook announced in [26]). We shall merely mention that it is accompanied by a pronounced promotion of the AOs in the bonding MO and substantial shielding of the nuclear charge for the formally weakly antibonding MO, with the result that the latter becomes strongly antibonding. In the light of these arguments, it is merely fortuitous that the one-electron MO theory works so well for H_2^+, H_2, and H_3^+.

[34] In the ground state of H_2, the MO ψ_+ (usually called $1\sigma_g$) is doubly occupied, and in the first excited state ψ_+ and ψ_- (also called $1\sigma_u$) are both singly occupied. Whereas in the ground state $1\sigma_g^2$ one electron necessarily has α spin and the other β spin, a triplet state with parallel spins and a singlet state with antiparallel spins are possible for the configuration $1\sigma_g 1\sigma_u$. The wave function of the triplet state ($^3\sum_\mu^-$) in the one-determinant approximation is

$$\frac{1}{\sqrt{2}} \begin{vmatrix} \psi_+(1)\,\alpha(1) & \psi_+(2)\,\alpha(2) \\ \psi_-(1)\,\alpha(1) & \psi_-(2)\,\alpha(2) \end{vmatrix} = \alpha(1)\,\alpha(2) \frac{1}{\sqrt{2}} \begin{vmatrix} \psi_+(1)\,\psi_+(2) \\ \psi_-(1)\,\psi_-(2) \end{vmatrix}$$

The wave function is thus the product of a spin function and a space function. We can confine the following discussion to the pure space function (8.1).

[35] The name "equivalent orbital" is due to *Lennard-Jones et al.* [*J. E. Lennard-Jones*, Proc. Roy. Soc. London *A 198*, 1, 14 (1949); *J. E. Lennard-Jones et al.*, *ibid. A 202*, 155, 166 (1950)], though the concept underlying the name is older [36]. Generalizations of the "equivalent orbitals" to situations where they are not definitely determined by the symmetry were given on the one hand by *S. F. Boys* [Rev. Mod. Phys. *32*, 296 (1960)], and on the other by *C. Edmiston* and *K. Ruedenberg* [Rev. Mod. Phys. *35*, 457 (1963)].

[36] *F. Hund*, Z. Phys. *74*, 1, 565 (1931). These are the fundamental articles on the subject of "localized bonds".

[37] *E.g.*: *E. Haselbach*, *E. Heilbronner*, *A. Mannschreck*, and *W. Seitz*, Angew. Chem. *82*, 879 (1970); Angew. Chem. internat. Edit. 9, 902 (1970). This article ends with the words "... that, in keeping with modern social trends, electrons also prefer to live in a commune, rather than in pairwise isolation". Attractive as this anthropomorphism appears, it is nevertheless false, since "pairing" or "living in a commune" are not really alternatives for electrons, and since PE spectroscopy does not yield information about the commune in the "ground state", but only shows how it reacts to the removal of one of its members.

[38] *G. Das* and *A. C. Wahl*, J. Chem. Phys. *47*, 2934 (1967).

[39] *P. E. Cade*, *K. D. Sales*, and *A. C. Wahl*, J. Chem. Phys. *44*, 1973 (1966).

[40] *M. Gelus*, *R. Ahlrichs*, *V. Staemmler*, and *W. Kutzelnigg*, Chem. Phys. Lett. *7*, 503 (1970); see also *J. H. Hall*, *D. S. Marynick*, and *W. N. Lipscomb*, Inorg. Chem. *11*, 3126 (1972).

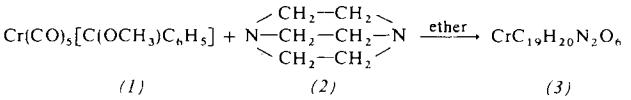
1,4-Diazabicyclo[2.2.2]octane(phenylmethoxy)-methylenepentacarbonylchromium(0), a Novel Nitrogen Ylide-Transition Metal Complex[1]

By *Fritz R. Kreissl, Ernst Otto Fischer, Cornelius G. Kreiter,* and *Karin Weiss*[*]

Primary and secondary amines replace the alkoxy group in alkoxycarbene complexes to form aminocarbene complexes. Kinetic studies have revealed that this reaction obeys a fourth order rate law[2]. A nitrogen ylide complex was assumed as an intermediate of the aminolysis.

The reaction of secondary and tertiary alkylphosphanes with alkoxy-, thio-, and selenocarbene complexes of chromium and tungsten at low temperature to give phosphorus ylide complexes[3–5] suggested that suitable tertiary amines should be able to form isolable nitrogen ylide complexes under similar conditions. Unlike primary and secondary amines, these would be incapable of further aminolytic reaction with the alkoxy group after having undergone nucleophilic addition to the carbene carbon. The postulated ylide intermediates should thus be isolable.

The reaction of red phenylmethoxycarbenepentacarbonylchromium(0) *(1)* with 1,4-diazabicyclo[2.2.2]octane *(2)* in diethyl ether led to a yellow diamagnetic crystalline powder which was characterized as a 1:1 addition product of *(1)* and *(2)* of the empirical formula $CrC_{19}H_{20}N_2O_6$ *(3)* by total analysis.



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

In aqueous $KHSO_4$ solution, *(3)* releases *(2)*; however, *(1)* is not regenerated but instead phenylhydroxycarbenepentacarbonylchromium(0) is found[6]. This result indicates that the original metal-carbene carbon bond of *(1)* is retained in the 1:1 complex and underlines the enhanced reactivity of the *O*-methyl group in the ylide complex.

The structure of *(3)* was determined from its IR, ^{1}H-NMR, and ^{13}C-NMR spectra.

The IR spectrum of a CH_2Cl_2 solution of *(3)* contains two absorptions at 2032 w and 1894 vs cm^{-1} in the νCO region which indicate the presence of a $Cr(CO)_5$ group.

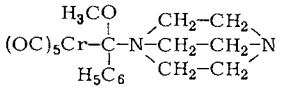
The ^{1}H-NMR spectrum of a [D_6]acetone solution of *(3)* exhibits four signals at $\tau = 2.62$ (m,5), 6.49 (m,6), 6.61 (m,6), and 6.74 (s,3). The first signal is ascribable to the phenyl protons, and the last one to the *O*-methyl protons. The signals at $\tau = 6.49$ and 6.61 form a characteristic AA'BB' spectrum, which is in full accord with addition of *(2)* to the carbene C atom of *(1)* *via* an N atom. The relative broadness of the lines precluded accurate determination of the coupling constants. The asymmetric C atom in *(3)* does not effect a visible signal splitting of the diastereotopic methylene protons which would lead to an ABCD system. The OCH_3 signal displays a considerable upfield shift compared to that of *(1)* (*trans*: $\tau = 4.88$, *cis*: $\tau = 5.78$). The resultant decrease of the electron deficiency at the coordinated carbene carbon atom on addition of *(2)* is also clear from a comparison of the ^{13}C-NMR spectra of *(1)* and *(3)* (Table 1).

Table 1. ^{13}C-NMR shifts (in ppm) of $Cr(CO)_5[C(OCH_3)C_6H_5]$ *(1)* in [D_6]benzene and $Cr(CO)_5C[(OCH_3)(C_6H_5)NC_6H_{12}N]$ *(3)* in [D_6]acetone; TMS as internal standard.

	CO_{cis}	CO_{trans}	Cr—C	C_6H_5	OCH_3	$N_2C_6H_{12}$
(1)	216.67	224.57	351.42	153.82 130.26 128.38 122.89	66.62	
(3)	223.75	228.50		155.80 128.06 124.39	51.78	54.39 45.63

In addition to the appearance of two new ^{13}C signals, corresponding to the added diamine, the 15-ppm upfield shift of the *O*-methyl carbon signal is particularly characteristic. No signal is observed for the former carbene carbon, presumably because of a prolonged relaxation time or interactions with the N atom.

In view of all the available data, compound *(3)* can be regarded as having the structure of a nitrogen ylide complex.



The reaction of *(1)* with trimethylamine under the same conditions as for *(2)* also leads to a yellow product that is under investigation at the present time.

Procedure:

$N(C_2H_4)_3N$ (0.56 g, 5 mmol) is added to a solution of $Cr(CO)_5[C(OCH_3)C_6H_5]$ (1 g, 3.2 mmol) in ether (20 ml) under nitrogen at room temperature. During 2 to 3 hours' stirring the solution becomes lighter and a yellow precipitate is formed. Addition of pentane (30 ml) completes the precipitation. The product is purified by dissolution in a little CH_2Cl_2 and reprecipitation with pentane. It is then taken up in a minimal volume of CH_2Cl_2 at room temperature and allowed to slowly recrystallize at −100 °C. Isolation at −60 °C on a cooled fritted glass funnel and subsequent drying (20 h) in a high vacuum at −30 °C affords a yellow powder, m.p. 101 °C; yield 0.88 g (65% based on *(1)*).

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[1] Transition Metal Carbene Complexes, Part 59. - Part 58: *E. O. Fischer* and *G. Kreis*, Chem. Ber., in press.

[2] *H. Werner, E. O. Fischer, B. Heckl,* and *C. G. Kreiter*, J. Organometal. Chem. *28*, 367 (1971).

[3] *F. R. Kreissl, C. G. Kreiter,* and *E. O. Fischer*, Angew. Chem. *84*, 679 (1972); Angew. Chem. internat. Edit. *11*, 643 (1972).

[4] *F. R. Kreissl, E. O. Fischer, C. G. Kreiter,* and *H. Fischer*, Chem. Ber. *106*, 1262 (1973).

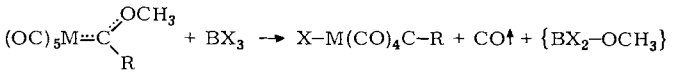
[5] *E. O. Fischer, F. R. Kreissl,* and *G. Kreis*, to be published.

[6] *E. O. Fischer, G. Kreis,* and *F. R. Kreissl*, J. Organometal Chem., in press.

trans-Halogeno[alkyl(aryl)carbyne]tetracarbonyl Complexes of Chromium, Molybdenum, and Tungsten —A New Class of Compounds Having a Transition Metal-Carbon Triple Bond[1]

By *Ernst Otto Fischer, Gerhard Kreis, Cornelius G. Kreiter, Jörn Müller, Gottfried Huttner*, and *Hans Lorenz*[*]

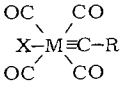
Methyl- or phenylmethoxycarbenepentacarbonyl complexes of chromium, molybdenum, and tungsten[2] react with boron trihalides (X=Cl, Br, I) in alkanes to give readily crystallizing, yellow to colorless thermolabile diamagnetic compounds of composition $XM(CO)_4CR$. It appears that the reaction involves simultaneous removal of the CH_3O group and a CO ligand and introduction of halogen into the complex according to:



$$(OC)_5M{=}C(OCH_3)R + BX_3 \rightarrow X{-}M(CO)_4C{-}R + CO\uparrow + \{BX_2{-}OCH_3\}$$

M = Cr, Mo, W; R = CH_3, C_6H_5; X = Cl, Br, I

The new complexes closely resemble one another in their mass spectroscopic behavior. The molecular ion $XM(CO)_4CR^+$ is invariably accompanied by a fragmentation pattern $XM(CO)_nCR^+$ with $n=3,2,1,0$. Only the phenyl derivatives with chromium as central metal atom give an intense peak at *m/e* 178 which we assign to tolan. This was the first indication that the new compounds might contain a *carbyne* ligand, *i.e.* a coordinated carbon atom bearing only an alkyl or aryl group. Dimerization of liberated phenylcarbyne ligands would explain the appearance of tolan in the mass spectrum. A second fragmentation series is observed for $Cl{-}W(CO)_4C{-}CH_3$ in which the molecule first loses the chlorine atom; not till then does successive loss of the four CO ligands take place. We consider the following arguments to substantiate



the proposed novel type of complex structure containing the sp hybridized C atom having two σ bonds to the organic alkyl or aryl group and to the metal at an angle of about 180°C and simultaneously participating in two additional $p_\pi-d_\pi$ bonds and thus maintaining the noble gas configuration at the metal atom manifested in the diamagnetism found experimentally for the complexes.

1. Total analyses established the composition $XM(CO)_4CR$ (X=Cl, Br, I; M=Cr, Mo, W; R=CH_3, C_6H_5).

2. All the mass spectra and two cryoscopic molecular weight determinations afforded relative molecular masses corresponding to monomeric structures.

3. The dipole moments (benzene, 20°C) lie between 4 and 6 D.

4. The IR spectra of the novel carbyne complexes all exhibit a very intense band (E) in the νCO region at about 2037–2051 cm^{-1} accompanied by a further weak to medium band (A_1) at about 2120 cm^{-1}. The number of bands and their intensity ratios provide unequivocal evidence for a *trans*-disubstituted tetracarbonyl complex $M(CO)_4L^1L^2$ with $L^1 \neq L^2$. The higher wave number shift of the maximum intensity band (E) relative to a comparable *trans*-substituted carbene complex such as $(C_6H_5)_3PCr(CO)_4[C(CH_3)(OCH_3)]$[3] amounts to about 150 cm^{-1}. The strong withdrawal of electrons from the metal atom by the carbyne ligand is compensated by the considerable charge transfer from the CO ligands to the metal, leading to an increase in the CO bond order and a marked short wave shift of the νCO frequencies. The νCO absorption of some carbyne complexes are listed in Table 1.

Table 1. IR spectra in the ν_{CO} region (*n*-hexane, cm^{-1}).

	A_1	E
$Br{-}W(CO)_4C{-}CH_3$	2125 s	2038 vs
$I{-}W(CO)_4C{-}C_6H_5$	2119 m	2037 vs
$Br{-}Cr(CO)_4C{-}C_6H_5$	2113 m	2051 vs
$I{-}Cr(CO)_4C{-}C_6H_5$	2106 m	2046 vs

5. The tungsten halogen frequencies in the far IR could be assigned for the somewhat more stable complexes $Br{-}W(CO)_4C{-}C_6H_5$, $I{-}W(CO)_4C{-}C_6H_5$, and $I{-}W(CO)_4C{-}CH_3$ (Table 2).

Table 2. FIR spectra in the ν MX region (cm^{-1}).

$Br{-}W(CO)_4C{-}C_6H_5$	ν_{W-Br}	180
$I{-}W(CO)_4C{-}C_6H_5$	ν_{W-I}	144
$I{-}W(CO)_4C{-}CH_3$	ν_{W-I}	144

6. ^{13}C-NMR studies also confirm our structural concept (Table 3). The almost constant position of the carbyne carbon resonance when the halogen is changed rules out bonding of the latter to the original carbene carbon, which has now become a carbyne carbon, and indicates direct metal-halogen coordination.

Table 3. ^{13}C-NMR shifts (CD_2Cl_2, ppm relative to TMS, internal).

	$C_{Carbyne}$	C_{CH_3}	C_{CO}
$Cl{-}W(CO)_4C{-}CH_3$	288.8	38.8	194.0
$Br{-}W(CO)_4C{-}CH_3$	288.1	38.6	192.7
$I{-}W(CO)_4C{-}CH_3$	286.3	38.0	191.7

In contrast, the following ^{13}C-NMR shifts are found for the $H_2C{=}CH{-}X$ system: X=Cl 126.0; X=Br 115.5; X=I 85.3 ppm[4].

The position of the ^{13}C resonance of the carbyne carbon at somewhat higher field strengths compared to that of the carbene carbon in the starting material is remarkable. The corresponding signals differ by about 45 ppm in the tungsten complexes and by about 20 ppm in the chromium complexes. The lower shielding in the chromium complexes compared with the tungsten complexes, suggests a drop in electronic stabilization; this probably accounts for their enhanced thermolability. Measurement of the carbon-carbon coupling constant in the complex $BrCr(CO)_4C{-}C_6H_5$ should reveal the carbyne carbon to be directly bonded to phenyl.

The carbon resonances of the CO ligands coincide in a single peak in all the compounds studied so far. Thus all the

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CO ligands are equivalent and the *trans* arrangement of the halogen and carbyne ligands already suggested by the IR spectrum is confirmed.

7. The ^{1}H-NMR spectra of the carbyne complexes measured in CD_2Cl_2 contain the expected signals. Some of them show considerable upfield shifts compared to the resonances of the corresponding carbene complexes[2] again evidencing the relatively high spin density at the carbyne carbon which is stabilized largely at the expense of the $M(CO)_4X$ group but hardly at all at the expense of the alkyl or aryl group. As particular feature of the $XW(CO)_4C{-}CH_3$ complexes, the methyl singlets are accompanied by satellites, which can be explained by coupling of the methyl protons with the tungsten isotope ^{183}W having a nuclear spin of 1/2.

Table 4. ^{1}H-NMR spectra, measured in CD_2Cl_2.

	$\tau_{C_6H_5}$	T[°C]		τ_{CH_3}	T[°C]
$Cl{-}W(CO)_4C{-}C_6H_5$	2.54 (s)	−15	$Cl{-}W(CO)_4C{-}CH_3$	7.77 (s)	−15
$Br{-}W(CO)_4C{-}C_6H_5$	2.45 (s)	−15	$Br{-}W(CO)_4C{-}CH_3$	7.88 (s)	−15
$I{-}W(CO)_4C{-}C_6H_5$	2.47 (m)	−15	$I{-}W(CO)_4C{-}CH_3$	8.12 (s)	−15
$Br{-}Mo(CO)_4C{-}C_6H_5$	2.43 (m)	−30	$Br{-}Cr(CO)_4C{-}CH_3$	7.42 (s)	−20
$Br{-}Cr(CO)_4C{-}C_6H_5$	2.45 (m)	−30	$I{-}Cr(CO)_4C{-}CH_3$	7.56 (s)	−15
$I{-}Cr(CO)_4C{-}C_6H_5$	2.28 (m)	−15			

8. The X-Ray structure analysis of $[(C_6H_5C)W(CO)_4I]$ backs up the other findings. (Space group Pbca; $a = 2010.3$, $b = 1211.8$, $c = 1126.4$ pm; $Z = 8$; $d_{exp.} = 2.46$, $d_{calc.} = 2.48$ g cm^{-3}; R factor presently: $R_1 = 0.11$ for 704 independent non-zero reflections.) The pseudooctahedral structure is reproduced in Figure 1.

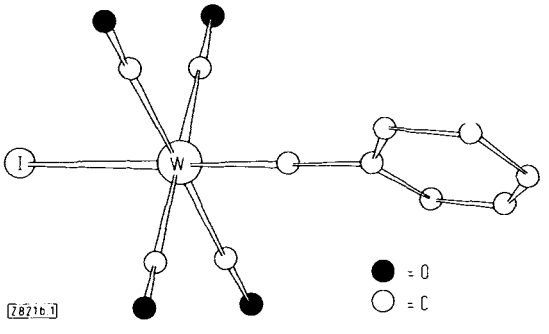

Fig. 1. Schematic representation of the molecular structure of $[(C_6H_5C)W(CO)_4I]$.

The distance of the carbyne carbon from tungsten of 188 ± 10 pm is shorter than the $W{-}C_{CO}$ distances (214 ± 10 pm), which in turn are somewhat larger than the corresponding distances in $W(CO)_6$ (205.8 ± 0.3 pm)[5]. The maximum deviation of the individual metal-ligand groups from the ideal linear arrangement is 20°. The d_{W-I} distance amounts to 284 ± 2 pm.

Procedure:

All operations should be carried out under nitrogen and with dried (Na, P_4O_{10}) and N_2-saturated solvents. A solution of methoxycarbene complex (2–3 g) in pentane (50 ml) is treated portion by portion with the boron trihalide (BBr_3 at *ca.* −15 °C, BCl_3 and BI_3 at *ca.* +10 °C). Rapidly ensuing decomposition necessitates further treatment of the reaction mixture at −20° to −40 °C.

The crude product obtained by drying in a high vacuum is purified by chromatography with pentane/methylene chloride on silica gel. If the reaction does not go to completion (possibly with BI_3), the starting complexes are eluted first whereas the new complexes migrate only slowly. After removal of the uppermost layer of silica gel elution is conducted at −30 °C and the eluate concentrated to about 1.5 ml at −20 °C *in vacuo*. Addition of pentane (10–15 ml) and cooling to −100 °C precipitates a finely crystalline deposit of the carbyne complexes. They are washed with pentane (*ca.* 4 ml, −100 °C) and dried (high vacuum, −20 °C, 1–2 d). The yields vary between 20 and 70%.

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[4] *G. E. Maciel*, J. Phys. Chem. *69*, 1947 (1965); *K. Hatada, K. Nagata*, and *H. Yuki*, Bull. Chem. Soc. Japan *43*, 3195, 3267 (1970).

[5] *S. P. Arnesen* and *H. M. Seip*, Acta Chem. Scand. *20*, 2711 (1966).

Tris(ethylene)nickel(0)

By *Karl Fischer, Klaus Jonas*, and *Günther Wilke*[*]

In 1872, *Zeise* discovered the first transition metal compound containing complexed ethylene $KPtCl_3 \cdot C_2H_4 \cdot H_2O$[1]. Most of the transition metal-olefin complexes to have been prepared since contain stabilizing ligands, *e. g.* phosphanes, in addition to the olefin. Binary complexes are known only with special kinds of olefins, such as cyclic polyolefins or those having a strained double bond. The first complexes of this type to be described were all-*trans*-1,5,9-cyclododecatrienenickel(0)[2] *(1)*, bis(1,5-cyclooctadiene)nickel(0)[2], and tris(bicycloheptene)nickel(0)[3].

We now wish to report the first binary metal-ethylene complex, tris(ethylene)nickel(0) *(2)*, which, like tetracarbonylnickel in the series of carbonyl-nickel complexes, can be regarded as the parent of all olefin-nickel(0) complexes.

Reaction of a deep red solution of *(1)* in diethyl ether with ethylene at 0 °C leads to a pale yellow solution whose ^{1}H-NMR spectrum shows that the cyclododecatriene (CDT) has been largely displaced from the nickel by ethy-

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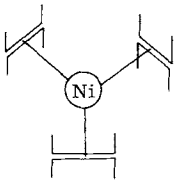
lene and that three ethylene molecules have become bonded to the nickel.

$$\underset{(1)}{\text{ttt-CDT—Ni(0)}} + 3C_2H_4 \rightarrow \underset{(2)}{(C_2H_4)_3Ni(0)} + \text{ttt-CDT}$$

On cooling of the solution to −78 °C, compound *(2)* crystallizes in the form of long colorless needles. The ^{1}H-NMR spectrum of the isolated complex *(2)* in deuteriotoluene at −30 °C exhibits a singlet for the ethylene protons at $\tau = 6.89$. If the solution contains additional free ethylene the signal experiences a downfield shift with simultaneous line broadening, which we attribute to exchange between free and complexed ethylene. The IR spectrum of *(2)* contains characteristic bands at 3065, 1511, and 1242 cm^{-1}. We assume that the three ligands adopt an approximately trigonal-planar arrangement around the central atom in tris(ethylene)nickel(0).



A similar arrangement of coordinated bonds is also assumed for all-*cis*-1,5,9-cyclododecatrienenickel(0)[4], and has been established by X-ray structure analysis[5] for tris(bicycloheptene)nickel(0).

The ethylene in *(2)* can again be displaced stepwise from the nickel. Equimolar amounts of $(C_6H_{11})_3P$ or $(C_6H_5)_3P$ yield the known complexes $(C_6H_{11})_3PNi(C_2H_4)_2$ and $(C_6H_5)_3PNi(C_2H_4)_2$[6] respectively. An excess of $(C_6H_5)_3P$ or $(C_6H_5O)_3P$ affords the corresponding $L_4Ni(0)$ complexes.

The new binary ethylene complex *(2)* reacts quantitatively with tri-*n*-butylaluminum at 0 °C yielding triethylaluminum and butene:

$$\underset{(2)}{Ni(C_2H_4)_3} + Al(C_4H_9)_3 \rightarrow Al(C_2H_5)_3 + 3C_4H_8 + Ni$$

The reaction occurs catalytically with an excess of ethylene and tri-*n*-butylaluminum. Apparently this reaction is the key step of the "nickel effect" discovered by *Ziegler* and *Holzkamp*[7].

Procedure:

The deep red solution of all-*trans*-CDT—Ni(0) *(1)* in ether (*ca.* 5 mmol/10 ml) is saturated with ethylene at −30 °C and then stirred at 0 °C for *ca.* 1 h until decolorized. On cooling to −78 °C *(2)* crystallizes but is usually contaminated with CDT and a little *(1)*. The crystalline mixture is dissolved in a small volume of cold ether and allowed to react further under ethylene at 0 °C for ½ h. On recooling to −78 °C, *(2)* precipitates as long colorless needles. The product is washed twice with liquid ethylene at −130 °C. Evaporation of the residual ethylene at −78 °C leaves analytically pure *(2)* in *ca.* 20% yield. The complex is stable up to 0 °C.

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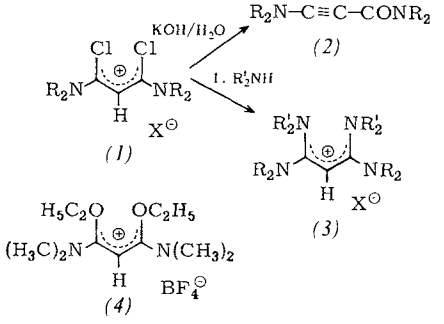
Allenetetramine and Dialkoxydiaminoallene

By *Heinz Günter Viehe* and *Zdenek Janousek*, together with *Rudolf Gompper* and *Dietrich Lach*[*]

The salts of 1,3-diamino-1,3-dichloroallyl cations such as *(1)* have become readily available by reaction of *N,N*-disubstituted acetamides and *N*-dichloromethylene-*N,N*-dialkylammonium chloride (phosgeneimmonium chloride)[1]. The action of alkalis on *(1)* affords ynamines, *e.g. (2)*, in 70% yield[2].



Treatment of *(1)* with secondary amines yields hydrolysis-resistant salts of 1,1,3,3-tetrakis(dialkylamino)allyl cations that can be isolated as perchlorates or chlorides, *e.g. (3a)*, $R = R' = CH_3$, $X = ClO_4$; *(3b)*, $R = R' = C_2H_5$, $X = Cl$.

Of comparable stability to the salts *(3a)* and *(3b)* is the salt *(4)*[3] obtained in crystalline form by alkylation of *N,N*-dimethyl-β-ethoxy-β-dimethylaminoacrylamide[4] with triethyloxonium tetrafluoroborate.

The cations of *(3)* and *(4)* may be regarded as protonation products of allenetetramine *(5)* and dialkoxydiaminoallene *(6)* respectively, which appear particularly interesting as electron-rich allenes whose reactivity should even exceed that of tetramercaptoallene[3,5] and tetramethoxyallene[6] (cf. [3,7,8]).

(3) and *(4)* can be converted into the allenes *(5)* and *(6)* either with *n*-butyllithium or, in the case of salts that are only soluble in polar solvents, with an excess of sodium amide in anhydrous liquid ammonia.

(5) and *(6)* are distillable, water-clear liquids that can be stored for days without decomposition in the absence of air and moisture. They react spontaneously with air, generating fumes. The hydrolysis of *(5b)*, leading to the amide *(7)*, and the reaction of *(6)*, affording the salt *(8)*, provide proof of the structures shown, as do the available spectral data.

(5a) undergoes an exothermic reaction with phenyl cyanate to give a salt that can be isolated as the perchlorate

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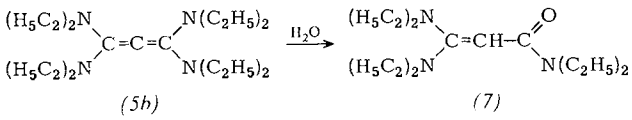
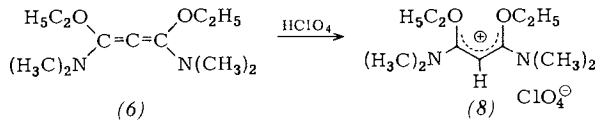
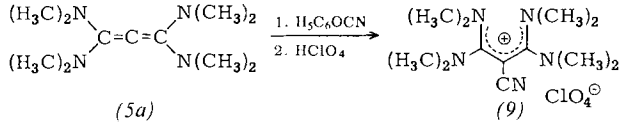


(5b) (7)



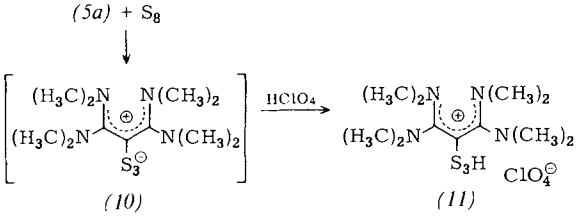
(6) (8)

(9). The low wave number of the split nitrile band at 2190 cm^{-1} is a striking feature of the IR spectrum of (9).



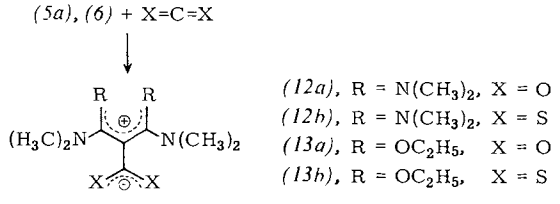
(5a) (9)

Reaction of (5a) with a suspension of sulfur in methylene chloride/ether occurs within an hour to give (10) which was isolated as (11) after protonation with perchloric acid.



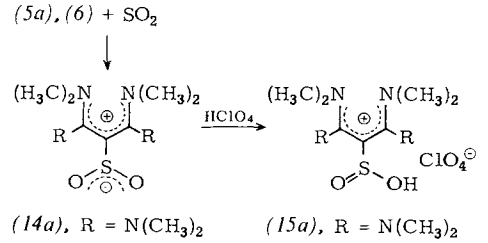
(10) (11)

Compounds (5a) and (6) react extremely readily and in good yields with carbon dioxide to give the dipolar adducts (12a) and (13a) respectively. Carbon disulfide affords (12b) and (13b). The four dipoles are stable for days in an inert gas atmosphere.



(12a), R = $N(CH_3)_2$, X = O
(12b), R = $N(CH_3)_2$, X = S
(13a), R = OC_2H_5, X = O
(13b), R = OC_2H_5, X = S

Reaction of (5a) and (6) with sulfur dioxide yields the products (14a) and (14b), respectively, which are only moderately stable or unstable at room temperature; they can be converted into the sulfinic acids (15a) and (15b) respectively on treatment with perchloric acid.



(14a), R = $N(CH_3)_2$ (15a), R = $N(CH_3)_2$
(14b), R = OC_2H_5 (15b), R = OC_2H_5

The above experiments show that the allenetetramines and the dialkoxydiaminoallenes are comparable in their reactivity with the ynamines[9] and the ethylenetetramines[10]

Tetrakis(diethylamino)allene (5b)

Butyllithium (6 ml, 1.7 M solution in light petroleum) was added dropwise to a stirred solution of 3,3-bis(diethylamino)-*N,N,N',N'*-tetraethylacrylamidinium chloride (3b)[11] (1.83 g, 5.65 mmol) in dry tetrahydrofuran (10 ml). The temperature of the mixture increased to the boiling point. After the addition was complete (*ca.* 5 min) the solvent was evaporated off without prior removal of precipitated LiCl. The residue was vacuum distilled (0.05 torr) as rapidly as possible. The procedure afforded 1.16 g (70%) of (5b) as a colorless oil having a strong characteristic odor; b.p. 110—120 °C/0.05 torr.

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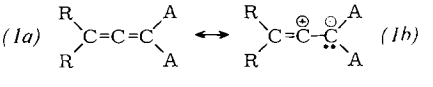
Cycloadditions of Electron-Deficient Allenes[**]

By *Rudolf Gompper* and *Dietrich Lach*[*]

Cycloadditions to electron-rich allenes are two-step reactions involving dipolar intermediates[1]; in a number of cases the reaction stops at the primary dipolar adducts[1,2]. Electron-deficient allenes (1) [A = electron-withdrawing group (−M effect)], for which a similar behavior is expected, exhibit a polarity related to that of ketenes[3], whose cycloadditions to olefins[4] can be described as concerted reactions[3,5] or as two-step reactions proceeding *via* dipolar intermediates[6,7]. By studying the cycloadditions of electron-deficient allenes to electron-rich multiple-bond systems, we hoped to obtain *inter alia* further insight into the mechanistic details of the cycloadditions of heterocumulenes.



(1a) (1b)

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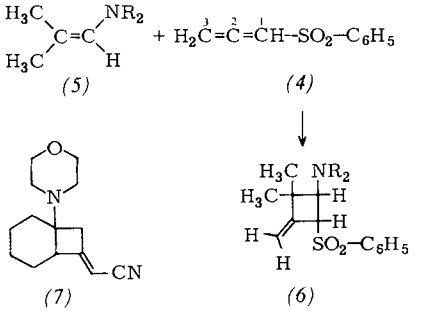
[**] Support of this work by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is gratefully acknowledged.

Whereas 1,1-bis(alkoxycarbonyl)allenes *(3)*[9], which are accessible from bis(alkoxycarbonyl)methylenetriphenylphosphoranes *(2)*[8] and diphenylketenes, display a disappointingly low reactivity, 1-benzenesulfonylallene *(4)*[10] reacts with aminoisobutenes *(5)* to give methylenecyclobutanes *(6)* [structural proof from NMR spectra; *(6a)*: R_2N—C—H $\tau = 7.31$ (1 H, d), SO_2—C—H $\tau = 5.63$ (1 H, m), $=CH_2$ $\tau = 4.90$ (2 H, m)].

$$(C_6H_5)_3P{=}C(CO_2R)_2 + (C_6H_5)_2C{=}C{=}O \rightarrow$$
(2)
$$(C_6H_5)_2C{=}C{=}C(CO_2R)_2 + (C_6H_5)_3PO$$
(3)
$R = CH_3, C_2H_5$

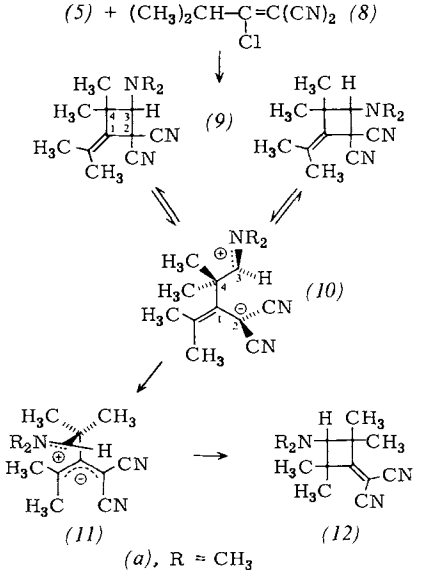
The cyclobutanes *(6)* are formed by cycloaddition to the C^1C^2 double bond of *(4)*. In contrast, the cyclobutane *(7)* arises by cycloaddition of morpholinocyclohexene[11] to the C^2C^3 bond of 1-cyanoallene[12].



(5) *(4)* *(7)* *(6)*

(a), R = CH_3
(b), R+R = $(CH_2)_4$

Attempted elimination of hydrogen chloride from 1-chloroisobutylidenemalodinitrile *(8)* with tertiary amines afforded only polymeric products. However, if *(8)* is treated with 2 equivalents of *(5)* then the isopropylidenecyclobutanes *(9)* can be isolated. In acetone, acetonitrile, and at elevated temperatures also in chloroform, but not in benzene, carbon tetrachloride, and cyclohexane, the compounds *(9)* give just one NMR signal for the two methyl groups at C^4.



(11) *(12)*

(a), R = CH_3
(b), R+R = $(CH_2)_4$

This phenomenon can be explained in terms of rapid equilibration between *(9)* and the zwitterion *(10)* (rapid rotation around the C^3C^4 bond). The coalescence temperature in $CDCl_3$ is 76 ± 1 °C for *(9a)* and 37 ± 1 °C for *(9b)*.

If a solution of *(9)* is allowed to stand, the appearance of the new cyclobutane *(12)* can soon be detected in the NMR spectrum. Conversion into *(12)* is complete after several hours' heating. The rearrangement of *(9)* into *(12)* most probably also proceeds *via* the dipole *(10)* (rotation around the C^1C^4 bond); the intermediacy of *(11)* also seems likely. The reaction is of first order; the activation energy determined between 55 and 75 °C amounts to $E_A = 11.1 \pm 1.0$ kcal/mol for *(9b)*.

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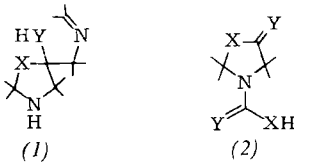
1,3-Anionic Cycloadditions of *trans,trans*-1,3-Diphenyl-2-azaallyllithium to Heterocumulenes[1][**]

By *Thomas Kauffmann* and *Rudolf Eidenschink*[*]

The accessibility of *trans,trans*-1,3-diphenyl-2-azaallyllithium *(5)* in amine- and lithium-amide-free solution by thermal ring cleavage of *N*-lithio-2,3-diphenylaziridine[3] has now made feasible studies on the behavior of *(5)* toward compounds undergoing ready irreversible addition of amines and lithium amides. We have reacted *(5)* with the heterocumulenes shown in the reaction scheme below. Since *(5)* adds normally to CO double bonds but undergoes cycloaddition to CN double bonds, and owing to the predictably high nucleophilicity of the anionic cycloadducts, we expected to obtain open-chain, cyclic, and bicyclic adducts, as well as the mixed types *(1)* and *(2)*.



(1) *(2)*

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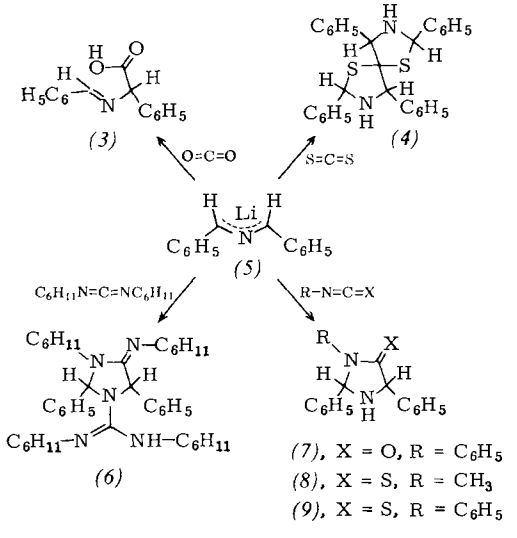
All expected structures except *(1)* were formed on adding an equimolar amount of the heterocumulene, as a THF solution either dropwise or in the solid state (CO_2) at −40 °C within 2 min, to an amine- and lithium-amide-free solution of *(5)* in THF/*n*-hexane (*ca.* 9:1) under nitrogen and allowing the components to react (see Table 1) in

Table 1. Products prepared.

	Product	Reaction temp. [°C]	time [a] [min]	Yield [%]	M.p. [°C]
(3)	2-(*N*-benzylideneamino)-phenylacetic acid	−60	60	*ca.* 50	— [5]
(4)	2,4,7,9-tetraphenyl-1,6-dithia-3,8-diaza-spiro[4.4]nonane	−40	3 (!)	31	154—155
(6)	3-cyclohexyl-4-cyclohexylimino-1-(*N,N'*-dicyclohexylamidino-2,5-diphenylimidazolidine	22 [b]	30	60	187
(7)	2,3,5-triphenyl-imidazolidin-4-one	−40	30	55	142
(8)	3-methyl-2,5-diphenyl-imidazolidine-4-thione	−40	30	46	[c]
(9)	2,3,5-triphenyl-imidazolidine-4-thione	−40	30	59	124

[a] The time required for the dropwise addition is not included.
[b] No reaction at −40 °C.
[c] B.p. 90 −95 °C/0.1 torr; m.p. (picrolonate) 171 °C.

the stirred mixture. After addition of water (at the temperature given) the products *(4)* and *(6)*—*(9)*, which have apparently not yet been described elsewhere, could be isolated, while the compound *(3)*, which has hitherto defied attempted isolation could be detected by degradation to α-aminophenylacetic acid. The compositions of the isolated compounds follow from elemental analysis and spectra (MS, NMR, IR). The configuration of the substituents at the chiral centers of *(4)* and *(6)*—*(9)* has not yet been established.



The reaction *(5)*→*(4)* represents the first example of 1,3-anionic cycloaddition to a CS double bond. Attempts to prepare the monocycloadduct of carbon disulfide were unsuccessful. Apparently the first step is slower than the second, as in the 1,3-dipolar cycloaddition of diphenylnitrile imine to carbon disulfide[6].

The cycloaddition to the asymmetric heterocumulenes proceeds predominantly or exclusively at the CN double bond, for no other products were detectable apart from the imidazolidine derivatives *(7)*—*(9)*[7].—Since only one diastereomeric form could be isolated in each case, in spite of careful column chromatographic work-up of the products, all the cycloadditions described are probably stereospecific.

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German version: Angew. Chem. 85, 583 (1973)

[1] 1,3-Anionic Cycloadditions, Part 8.—Part 7: [2].

[2] *R. Eidenschink* and *Th. Kauffmann*, Angew. Chem. *84*, 292 (1972); Angew. Chem. internat. Edit. *11*, 292 (1972).

[3] *Th. Kauffmann, K. Habersaat*, and *E. Köppelmann*, Angew. Chem. *84*, 262 (1972); Angew. Chem. internat. Edit. *11*, 291 (1972).

[4] *Th. Kauffmann, H. Berg, E. Ludorff*, and *A. Woltermann*, Angew. Chem. *82*, 986 (1970); Angew. Chem. internat. Edit. 9, 960 (1970).

[5] Detected by hydrolysis with dilute acetic acid to give the known α-aminophenylacetic acid [43%, based on *(5)*]. The reaction of *(5)* with carbon dioxide was performed by *U. Brandl* (Münster 1973).

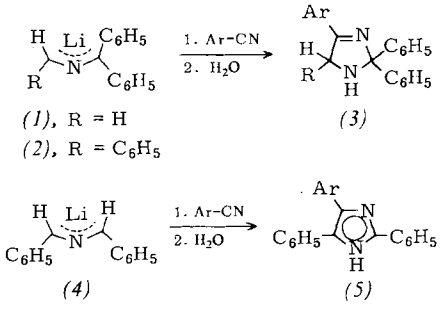
[6] *R. Huisgen, R. Grashey, M. Seidel, H. Knupfer*, and *R. Schmidt*, Liebigs Ann. Chem. *658*, 169 (1962).

[7] A corresponding regiospecificity has also been observed in 1,3-dipolar cycloadditions to isocyanates and isothiocyanates. The 1,3-dipole diphenylnitrile imine, on the other hand, undergoes cycloaddition to equal extents to the CN and CS double bonds of phenyl thiocyanate: cf. *R. Huisgen*, Angew. Chem. *75*, 604 (1963); Angew. Chem. internat. Edit. *2*, 565 (1963).

1,3-Anionic Cycloaddition of 2-Azaallyllithium Compounds to Nitriles[1][**]

By *Thomas Kauffmann, Alfred Busch, Kai Habersaat*, and *Edgar Köppelmann*[*]

We have found that 2-azaallyllithium compounds undergo cycloaddition to aromatic nitriles to give either 3-imidazolines *(3)* or, as a result of a secondary reaction that is presumably initiated by elimination of lithium hydride[3], imidazoles *(5)*. "Enolizable" nitriles such as propio- or butyronitrile were found to be unsuitable as 1,3-anionophiles (0 or 1% cycloadduct formation respectively). Such nitriles are probably deactivated by α-lithiation with concomitant consumption of the azaallyllithium compound.



In two cases aromatic nitriles gave rise to open chain products. These 4-amino-2-azabutadienes, whose enamine structure *(6)* has been established by spectroscopy, are labile yellowish red substances which polymerize within a few days on exposure to air. As far as we know, enamines

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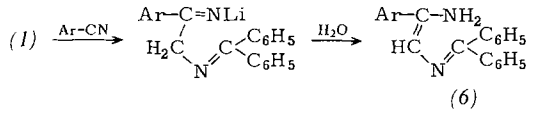
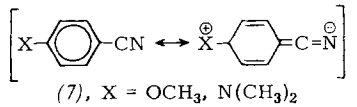
[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

of this kind—unsubstituted amino group and CC double bond conjugated with a CN double bond—are new[4].

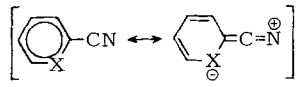


(6)

Since 1,1-diphenyl-2-azaallyllithium (1) undergoes cycloaddition to nitriles containing a group displaying a +M effect, whereas only normal addition takes place with the nitriles (8), the cycloaddition would appear to require a relatively high electron density at the nitrile nitrogen.



(7), X = OCH_3, $N(CH_3)_2$



(8), X = N, CH

The 2-azaallyllithium compounds (1), (2), and (4) were prepared from azomethines and lithium diisopropylamide in solution (THF/*n*-hexane, *ca.* 5:1)[5]. To these stirred solutions were added equimolar amounts of the nitriles in THF at −60 °C. Further details regarding execution of the reaction may be seen in Table 1. The composition

Table 1. Products prepared.

	Reactants	Product	Yield [%]	M.p. [°C]
(1) +	*m*-tolunitrile [a]	(3a) 2,2-diphenyl-4-(3-tolyl)-3-imidazoline	31	307—308
(1) +	*p*-methoxybenzonitrile [a]	(3b) 2,2-diphenyl-4-(4-methoxyphenyl)-3-imidazoline	47	124
(1) +	*p*-dimethylaminobenzonitrile [b]	(3c) 2,2-diphenyl-4-(4-dimethylaminophenyl)-3-imidazoline	42	152—153
(2) +	benzonitrile [a]	(3d) 2,2,4,5-tetraphenyl-3-imidazoline	10	203—204
(4) +	benzonitrile [b]	(5a) 2,4,5-triphenylimidazole	52	273
(4) +	*m*-tolunitrile [a]	(5b) 2,4(5)-diphenyl-5(4)-(3-tolyl)imidazole	50	278—279
(4) +	*p*-tolunitrile [a]	(5c) 2,4(5)-diphenyl-5(4)-(4-tolyl)imidazole	52	229—230
(4) +	nicotinonitrile [a]	(5d) 2,4(5)-diphenyl-5(4)-(3-pyridyl)imidazole	47	215—216
(4) +	butyronitrile [c]	(5e) 2,4(5)-diphenyl-4(5)-propylimidazole	1	143—144
(1) +	benzonitrile [a]	(6a) 4-amino-1,1,4-triphenyl-2-azabutadiene	65	148—150
(1) +	2-cyanopyridine [a] azabutadiene	(6b) 4-amino-1,1-diphenyl-4-(2-pyridyl)-2-	26	(oil) picrate 113—116

[a] Stirred for 18 h at 20 °C after addition of nitrile.
[b] Stirred for 12 h at 20 °C and 3 h at 50 °C after addition of nitrile.
[c] Stirred for 20 h at 20 °C and 4 h at 60 °C after addition of nitrile.

of the products obtained by hydrolysis with water, which do not appear to have been described previously with the exception of 2,4,5-triphenylimidazole (5a), follows from elemental analysis, molecular weight determinations, and spectra (NMR, IR, MS).

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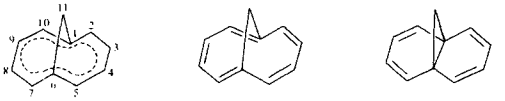
[1] 1,3-Anionic Cycloaddition, Part 9.— Part 8: [2].
[2] *Th. Kauffmann* and *R. Eidenschink*, Angew. Chem. *85*, 583 (1973); Angew. Chem. internat. Edit. *12*, 568 (1973).
[3] For an analogous secondary reaction on 1,3-anionic cycloaddition to tolan see [5].
[4] Corresponding enamines having the CC double bond conjugated with a CO double bond or a CN triple bond are known: *G. O. Dudek* and *R. K. Holm*, J. Amer. Chem. Soc. *84*, 2691 (1962); *S. Baldwin*, J. Org. Chem. *26*, 3288 (1961).
[5] *Th. Kauffmann*, *H. Berg*, and *E. Köppelmann*, Angew. Chem. *82*, 396 (1970); Angew. Chem. internat. Edit. *9*, 380 (1970).

An Aromatic-Olefin Equilibrium: 1,6-Methano-[10]annulene-Tricyclo[4.4.1.0^{1,6}]undeca-2,4,7,9-Tetraene Valence Tautomerism[**]

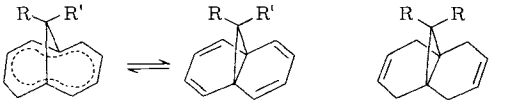
By *Harald Günther*, *Hans Schmickler*, *Wolfgang Bremser*, *Franz A. Straube*, and *Emanuel Vogel*[*]

Numerous physical studies concur in indicating 1,6-methano[10]annulene (1) to possess a delocalized π-electron decet[1,2]. Alternative olefinic structures such as (2) or (3) can however become important in derivatives of (1). Thus our knowledge of the norcaradiene-cycloheptatriene system[3] suggests that (3), as "double norcaradiene", is an attractive valence tautomeric structure for 1,6-methano[10]annulenes bearing suitable substituents at C-11.



(1) (2) (3)

Such systems may also be expected to undergo rapid reversible valence tautomerization of type (4)⇌(5)[4].



(4) (5)

(4a) ⇌ (5a), R = R' = CH_3 (6), R = H
(4b) ⇌ (5b), R = CH_3, R' = CN (7), R = CH_3
(4c) ⇌ (5c), R = $CH_2C_6H_5$, R' = CN

Evidence favoring the last alternative has been provided in particular by the behavior of 11,11-disubstituted 1,6-methano[10]annulenes[5] and the spectroscopic data of the dimethyl compound (4a)[4]: in the ^{1}H-NMR spectrum of (4a) the peripheral protons (δ = 6.22, 6.11) are shielded by *ca.* 1 ppm compared to those of (1)[2c], and the ^3J values [J(2,3) = 9.78, J(3,4) = 6.85 Hz] resemble the corresponding constants in the 1,3-cyclohexadiene system[6].

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[**] Applications of ^{13}C-Resonance Spectroscopy, Part 6.—Part 5: ref. [11]. Generous support of this work by the Deutsche Forschungsgemeinschaft and the Fonds der chemischen Industrie is gratefully acknowledged.

In the UV spectrum[4] the extinction of the long-wave band at 350–400 nm[2a,f] characteristic of *(1)* has decreased significantly [*(1)*: ε(385)=135[2a]; *(4a)*: ε(385)=39, both in cyclohexane][7].

We have now been able to establish the existence of fluxional systems of type *(4)*⇄*(5)* by variable-temperature ^{13}C-NMR measurements (Table 1, Fig. 1)[8]. Mere consideration of the high position of the C-1,6 resonance of *(4a)* at 35 °C [δ=81.7 ppm; Δσ=+32.9 ppm compared to *(1)*[9]] suggests time averaging[10]. C-11 in *(4a)* (δ=16.9 ppm) is considerably more shielded than in *(1)* (Δσ=+17.9 ppm), although the methyl groups should have a deshielding effect as indicated in particular by the data pertinent to the systems *(6)* and *(7)*. Lowering the temperature leads to a downfield shift both for the absorption of C-1,6 and for that of C-11. This confirms that the aromatic structure *(4a)* is the more stable one. Predictably, the resonances of the other C atoms that are sp^2 hybridized in both isomers are affected only slightly.

C-1,6 and C-11 are subject to even more pronounced shielding in 11-cyano-11-methyl-1,6-methano[10]annulene *(4b)*⇄*(5b)*[12], in which the resonance of C-1,6 is found beyond the region typical for sp^2 hybridized C atoms. This observation accords with the expected substituent effect of the cyano group, as π-acceptor and stabilizer of three-membered rings[3], on the valence tautomerism. It is interesting that the temperature effect is opposed to that for the system *(4a)*⇄*(5a)*. Accordingly, the tetraene *(5b)* is more stable than the [10]annulene *(4b)*. The highest C-1,6 resonance to be observed so far was found for 11-benzyl-11-cyano-1,6-methano[10]annulene *(4c)*⇄*(5c)*[13].

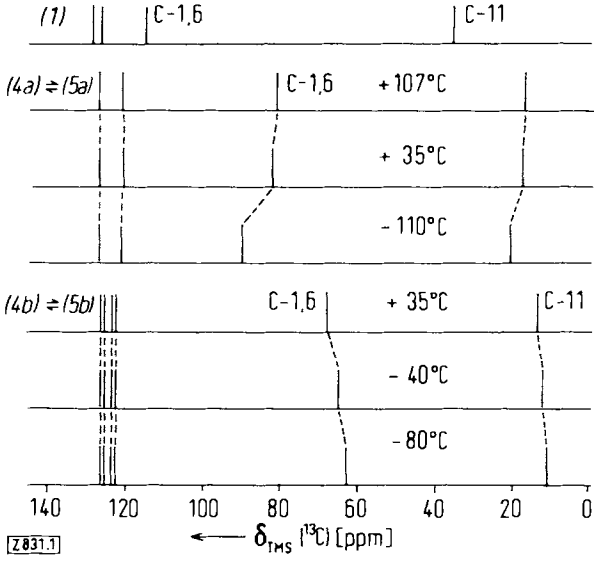

Fig. 1. Schematic representation of the ^{13}C-NMR spectra of *(1)* and the fluxional systems *(4a)*⇄*(5a)* and *(4b)*⇄*(5b)*; tetramethylsilane as internal standard.

The ^{13}C-NMR frequencies of the parent system *(1)* change only insignificantly with temperature. However, as for the norcaradiene-cycloheptatriene system, the findings for the substituted compounds indicate that a certain equilibrium concentration of the valence-tautomeric "norcaradiene", *i.e.* tricyclo[4.4.1.0^{1,6}]undeca-2,4,7,9-tetraene *(5)*, where R=R′=H, will be present, even though its contribution may be minimal[14].

It has not yet been possible to slow down the rate of the valence tautomerization *(4)*⇄*(5)* sufficiently to permit observation of the individual ^{13}C-NMR spectra of the two isomers. It may therefore be assumed that the energy barrier of the rearrangement is extremely low[16]. This appears understandable in view of the relatively small distance between C-1 and C-6 in *(1)* (2.26 Å) which favors formation of the cyclopropane bond[17].

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German version: Angew. Chem. 85, 585 (1973)

[1] *E. Vogel* and *H. D. Roth*, Angew. Chem. *76*, 145 (1964); Angew. Chem. internat. Edit. *3*, 228 (1964).

[2] a) ESR: *F. Gerson, E. Heilbronner, W. A. Böll*, and *E. Vogel*, Helv. Chim. Acta *48*, 1494 (1965); b) electron diffraction: *L. K. Montgomery* and *J. Croetzer* personal communication; c) ^{1}H-NMR: *H. Günther*, Z. Naturforsch. *20b*, 948 (1965); d) X-ray structure analysis: *M. Dobler* and *J. D. Dunitz*, Helv. Chim. Acta *48*, 1429 (1965); e) photoelectron spectrum: *R. Boschi, W. Schmidt*, and *J.-C. Gfeller*, Tetrahedron Lett. *1972*, 4107; f) UV: *H.-R. Blattmann, W. A. Böll, E. Heilbronner, G. Hohlneicher, E. Vogel*, and *J.-P. Weber*, Helv. Chim. Acta *49*, 2017 (1966); g) enthalpy of formation: *W. Bremser, R. Hagen, E. Heilbronner*, and *E. Vogel*, *ibid. 52*, 418 (1969); h) dipole moments: *W. Bremser, H. T. Grunder, E. Heilbronner*, and *E. Vogel*, *ibid 50*. 84 (1967).

[3] a) *M. Görlitz* and *H. Günther*, Tetrahedron *25*, 4467 (1969); b) *E. Ciganek*, J. Amer. Chem. Soc. *93*, 2207 (1971); *E. Vogel, W. Wiedemann, H. D. Roth, J. Eimer*, and *H. Günther*, Liebigs Ann. Chem. *759*, 1 (1972), and further literature cited therein.

[4] *E. Vogel*, Pure Appl. Chem. *20*, 237 (1969); *E. DeCleur*, Dissertation, Universität Köln 1969.

[5] *V. Rautenstrauch, H.-J. Scholl*, and *E. Vogel*, Angew. Chem. *80*, 278 (1968); Angew. Chem. internat. Edit. *7*, 288 (1968).

Table 1. ^{13}C-NMR data of compounds *(1)* and *(4)*–*(7)*; δ_{TMS} values in ppm [a].

Cpd.	T [°C]	C-1,6	C-2,5,7,10	C-3,4,8,9	C-11	CH_3	CN	CH_2	Solvent/lock
(1) [b]	+35	114.6	128.7	126.1	34.8	—	—	—	CS_2/[D_6]-acetone
	−110	113.7	128.6	125.9	34.2	—	—	—	CS_2/[D_6]-acetone
(4a)⇄*(5a)*	+107	79.8	126.9	120.7	16.2	17.3	—	—	C_4Cl_6/[D_8]-dioxane
	+35	81.7	126.7	120.6	16.9	17.2	—	—	CS_2/$CDCl_3$
	−110	89.3	126.3	120.8	20.0	17.1	—	—	CS_2/$CDCl_3$
(4b)⇄*(5b)*	+35	67.1	126.9 126.2 124.5 123.2		13.6	12.5	119.0	—	CD_2Cl_2
	−40	64.6	127.0 126.1 124.5 122.8		12.2	12.0	119.5	—	CD_2Cl_2
	−80	62.6	127.2 126.2 124.5 122.7		11.3	11.7	119.9	—	CD_2Cl_2
(4c)⇄*(5c)*	+30	57.8	8 signals between 137.8		14.9	—	118.0	29.9	CD_2Cl_2
	−80	54.0	(137.6) and 123.2 (122.7)		12.9	—	118.3	28.7	CD_2Cl_2
(6)		20.1	31.9	124.4	12.9	—	—	—	$CDCl_3$
(7)		18.1	31.4	125.7	21.6	17.0	—	—	$CDCl_3$

[a] All spectra were recorded using the Fourier transform technique with broad band ^{1}H decoupling; measuring frequency 22.6 MHz, Bruker HX-90 spectrometer.

[b] Cf. also ref.[9]; the assignments of all ^{13}C resonances have meanwhile been confirmed experimentally by the observation of typical fingerprints in the non-decoupled spectrum according to ref.[11].

[6] *H. Günther* and *H.-H. Hinrichs*, Liebigs Ann. Chem. *706*, 1 (1967).

[7] There is still some uncertainty as to the correct interpretation of the C-1—C-6 distance in solid *(4a)* (1.80 Å) found by X-ray structural analysis (*R. Bianchi, A. Mugnoli*, and *M. Simonetta*, Chem. Commun. *1972*, 1073).

[8] ^{13}C-NMR spectroscopy [10] proves superior to ^{1}H-NMR spectroscopy in this case because the C-1,6 and C-11 resonances are more sensitive probes for the valence tautomerism *(4)*⇌*(5)*. The changes in the resonance frequencies due to chemical exchange amount to *ca.* 2000 Hz (C-1,6) but less than 100 Hz in ^{1}H-NMR spectroscopy (peripheral protons). Moreover, the ^{13}C-NMR spectra are not complicated by spin-spin coupling. Previous ^{1}H-NMR spectra accordingly did not lead to clear-cut results.

[9] *H. Günther, H. Schmickler, H. Königshofen, K. Recker*, and *E. Vogel*, Angew. Chem. *85*, 261 (1973); Angew. Chem. internat. Edit. *12*, 243 (1973).

[10] *H. Günther* and *T. Keller*, Chem. Ber. *103*, 3231 (1970).

[11] *H. Günther, H. Schmickler*, and *G. Jikeli*, J. Magn. Resonance, in press.

[12] *E. Vogel* and *V. Rautenstrauch*, unpublished.

[13] Synthesis: *E. Vogel* and *F. A. Straube*, to be published.

[14] In 11,11-dimethylene-1,6-methano[10]annulene [13] C-1 and C-6 are deshielded in comparison with *(1)* (δ = 123.2 ppm). Here the introduction of the three-membered ring could effect opening of the angle C-1—C-11—C-6 and thereby increase the distance between C-1 and C-6. It has not yet been established whether the deshielding is the result of an equilibrium shift or a manifestation [15] of the separation-dependent overlapping of the $2p_z$ orbitals on C-1 and C-6 in the aromatic system which has been detected experimentally[2a,e,f]. A "normal" substituent effect (replacement of the H atoms at C-11 by —CH_2—CH_2—) could also be responsible for the deshielding, although the findings for *(6)* and *(7)* make this possibility appear rather unlikely.

[15] Cf. *A. V. Kemp-Jones, A. J. Jones, M. Sakai, C. P. Beeman*, and *S. Masamune*, Can. J. Chem. *51*, 767 (1973).

[16] In one case we found a barrier ΔG^{*} of 8—9 kcal/mol for the comparable norcaradiene-cycloheptatriene system[3a]. Here the splitting of the ^{13}C resonances was observed already at *ca.* −90 °C. (*H. Günther, W. Peters*, and *R. Wehner*, unpublished). Since no line broadening could be detected for *(4a)*⇌*(5a)*, even at −110 °C, the known relationship between coalescence temperature and free energy of activation affords $\Delta G^{*} < 6.6$ kcal/mol for a δν value of 2000 Hz[8,10] for this system.

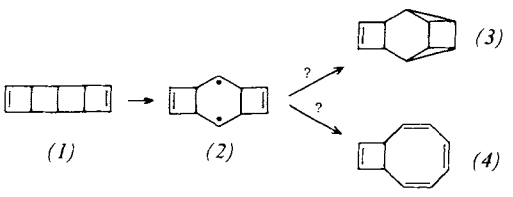
[17] Since this is to our knowledge the first case of valence tautomerism between an aromatic compound and an olefin the energetics of the system *(4)*⇌*(5)* are of particular interest. A ΔH° value of the order of 0.2 kcal/mol in favor of *(4a)* can be estimated from the ^{13}C data of *(4a)*⇌*(5a)*. The question whether the dynamic process can also be ascribed to a valence tautomerism of the type *(2)*⇌*(3)* cannot be answered by ^{13}C-NMR spectroscopy. However, this possibility can be ruled out on the basis of the UV spectra, which exhibit bands characteristic of the delocalized 10π system[2a,f] in all case . (We are grateful to Dr. *W. A. Böll* for a discussion on this point.)

Thermolysis of the Tetracyclo[4.4.0.0^{2,5}.0^{7,10}]-deca-3,8-diene System. π-Homoconjugation or σ-Hyperconjugation?[**]

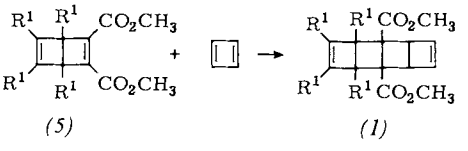
By *Hans-Dieter Martin* and *Mirko Hekman*[*]

In the present communication we report the differing thermolytic behavior of two representatives of the $(CH)_{10}$ system *(1)*[1], namely *(1a)* and *(1b)*. It was of particular interest to establish whether an intermediate 1,4-diradical *(2)*[2] undergoes stabilization by intramolecular cycloaddition to a double bond to give *(3)*, in the same way as a number of 1,3-diradicals[3], or fragmentation with cleavage of a σ bond to give *(4)*.

(1a) is not accessible from *(6)* by photochemical butadiene-cyclobutene isomerization[4]. We synthesized



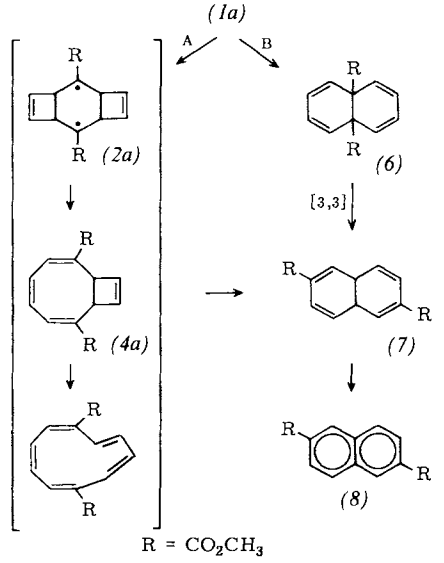
(1a) from the Dewar benzene *(5a)* and cyclobutadiene, and obtained the product as colorless crystals of m.p. 61—63 °C (from pentane) [NMR (60 MHz, CCl_4): 3.72 (4H, m), 6.40 (6H, s), 6.72 τ (4H, m); mass spectrum: $m/e = 246$ (M^+)].



(a), R^1 = H; *(b)*, R^1 = CH_3

The final product of thermolysis (50—80 °C in CCl_4) of *(1a)* is 9,10-dihydronaphthalene *(7)* [NMR ($CDCl_3$): τ = 2.90 (2H, m), 3.45 (2H, d, J_{AB} = 9.5 Hz), 3.85 (2H, d, J_{AB} = 9.5 Hz), 6.20 (6H, s), 6.93 (2H, m); UV in CH_3CN: $\lambda_{max}(\varepsilon)$ = 285 nm (≈ 2600[5])]. According to the UV spectrum the two six-membered rings in *(7)* must be *trans*-fused [the unsubstituted 9,10-dihydronaphthalenes differ drastically in their electronic spectra; $\lambda_{max}(\varepsilon)$: *cis* 248 nm (4072)[6], *trans* 276 nm (3850)[7]].

Compound *(7)*, the only defined thermolysis product, readily aromatizes to 2,6-bis(methoxycarbonyl)naphthalene *(8)*, which was found to be identical with an authentic sample. Formation of *(7)* could follow route A or B. It appears improbable that route B is operative [particularly as *cis*-fused *(7)* would then be expected] since thermolysis of *(6)*[8] gives a mixture of several dihydronaphthalenes. Moreover, the radical-stabilizing methoxycarbonyl groups favor cleavage according to A.



The geometry of *(1a)* is unknown. Alternatives *(1a)*-I and *(1a)*-III can be ruled out with some degree of certainty on the basis of the NMR spectrum. Double resonance experiments show that irradiation at τ = 6.72 causes the

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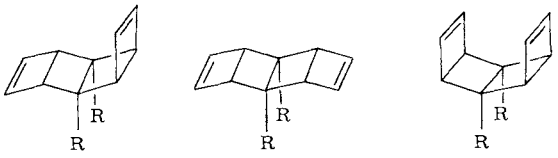
[**] We are grateful to the Deutsche Forschungsgemeinschaft for financial support.—Part 5 of "Small Rings".—Part 4: *H.-D. Martin* and *M. Hekman*, Angew. Chem. *84*, 995 (1972); Angew. Chem. internat. Edit. *11*, 926 (1972). Part 3: [3].

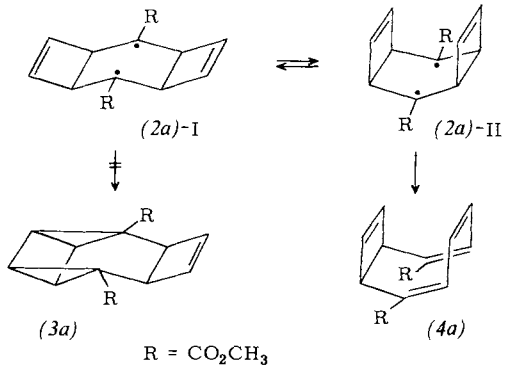
multiplet at $\tau = 3.72$ to collapse to a singlet at $\tau = 3.72$ ($W_H = 0.7$ Hz). This can be regarded as an argument against *(1a)*-I. The olefinic protons of *(1a)*-III would be expected at considerably higher field ($\tau \approx 4.5$—4.8[9]).



(1a)-I *(1a)*-II *(1a)*-III

R = CO_2CH_3

No intramolecular cycloaddition of *(2a)* to give *(3a)* is observed. Instead the findings can be interpreted in the following way: the diradical *(2a)* exists as two conformers *(2a)*-I and *(2a)*-II.



(2a)-I *(2a)*-II *(3a)* *(4a)*

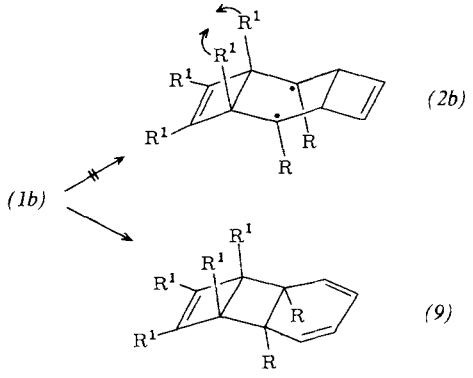
R = CO_2CH_3

Through-space interaction[10] between the radical centers and the double bonds in *(2a)*-I would be permitted by the prevailing geometry (π-homoconjugation) and could be responsible for the formation of *(3a)*; however, no such interaction is actually observed. On the other hand, through-bond interaction[10,11] of the radical centers *via* the intermediate σ bond (hyperconjugation) cannot be neglected in either conformation. If this kind of conjugation dominates then fragmentation to give *(4a)* will be promoted. This is the case in the situation under study. The fact that thermolysis of bicyclo[2.2.0]hexanes[12] predominantly yields *cis,trans*-dienes can be explained in terms of the chair conformation of the intermediate diradical. However, *(2a)*-II is unable to exist in such a conformation.

Further support for route A comes from the thermolysis of the tetracycle *(1b)* obtained from *(5b)* and cyclobutadiene. [*(1b)*, NMR ($CDCl_3$): $\tau = 3.70$ (2H, m), 6.36 (6H, s), 6.59 (2H, m), 8.50 (6H, s), 8.89 (6H, s); mass spectrum: $m/e = 302$ (M^+); m.p. 91—92 °C (from pentane)].

Compound *(1b)* exhibits a considerably greater thermal stability than *(1a)*. Fragmentation does not occur below 150 °C, the major product being dimethyl phthalate which presumably arises by opening of the unsubstituted cyclobutene ring in *(1b)* to give *(9)* followed by Alder-Rickert cleavage. Under the drastic reaction conditions necessary it was impossible to detect *(9)*. The mutual steric hindrance of the two methyl groups in *(2b)* increases the activation energy for the formation of this radical compared to the reaction *(1a)* → *(2a)*; ring cleavage to give *(9)* dominates.

The kinetics of thermolysis of *(1a)* in perchlorobutadiene were measured between 50 and 80 °C. The parameters



(2b) *(1b)* *(9)*

R = CO_2CH_3, $R^1 = CH_3$

obtained by the method of least squares ($E_a = 24.5$ kcal/mol, $\log A = 12.0$, $\Delta S^{\neq} = -5.8$ cal deg^{-1} mol^{-1}, $\Delta H^{\neq} = 23.8$ kcal/mol, $\Delta G^{\neq} = 25.7$ kcal/mol at $T_m = 338$ °K) also evidence a unimolecular decomposition by route A and not by route B since $E_a \geq 27$ kcal/mol and $\log A \approx 14$[13] would be expected for cleavage of a cyclobutene ring in *(1a)*. This would be inconsistent with the negative activation entropy observed, which can however be satisfactorily interpreted by formation of a resonance stabilized diradical *(2a)*. The lowering of the activation energy compared with bicyclo[2.2.0]hexane ($E_a = 36$ kcal/mol) is readily explained by the effect of the methoxycarbonyl groups.

Owing to the occurrence of side reactions the kinetics of thermolysis of *(1b)* are more complicated. The consumption of *(1b)* (Σk_i) affords an apparent activation energy ($\Sigma k_i E_i / \Sigma k_i$) $E_a = 34$ kcal/mol and $\log A = 14.4$. Since formation of dimethyl phthalate is the main reaction one can write $k_{(1b)\rightarrow(9)} = k_1 > k_2, k_3 \ldots$ The parameters measured for the consumption of *(1b)* are thus an approximation for the values corresponding to the reaction *(1b)* → *(9)*; the decomposition of *(9)* is certainly not rate-determining. The difference between the *A* factors $10^{12.0}$ and $\approx 10^{14}$ for *(1a)* and *(1b)* respectively also clearly underlines the difference in thermolysis mechanisms. The route proposed for *(1b)* is in full accord with $\log A \approx 14$[13]. The cleavage of the basic system of *(9)* with aromatization is not unexpected[14].

The behavior of the 1,4-diradical *(2a)* is therefore consistent with theory[11], unlike that of 1,3-diradicals whose intramolecular cycloaddition[3] (controlled by π-homoconjugation) can become the sole reaction path.

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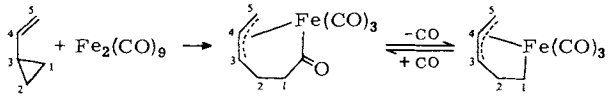
Metal-Catalyzed [4+2]-Cycloaddition of a Vinylcyclopropane Group to a C—C Bond of a Cyclopropane Ring: Synthesis and Degenerate Valence Isomerization of a Bishomobenzene-Fe(CO)$_3$ Derivative[1]

By *Rudolf Aumann*[*]

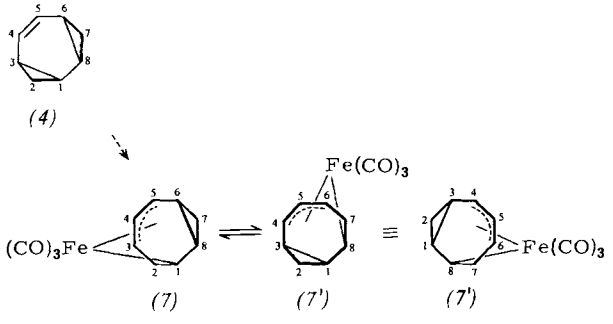
Cycloaddition of vinylcyclopropane groups *(1)* to carbonyliron-carbon bonds affords Fe-heterocycles *(2)* that decompose reversibly into 1,3,4,5-η-pentenediyl-Fe(CO)$_3$ compounds *(3)* and carbon monoxide[2,3].



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

Systems of type *(3)* are potential intermediates in hitherto unknown metal-catalyzed [4+2]-cycloadditions of vinylcyclopropane systems to unsaturated C—C bonds.

I have synthesized a model compound *(7)* in which an intramolecular addition of the C^6—C^8 bond of the cyclopropane ring to the 1,3,4,5-η-Fe(CO)$_3$ unit can be recognized by a degenerate valence isomerization *(7)*⇌*(7')*.

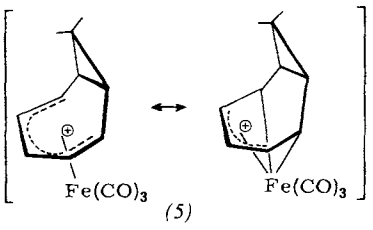


(4)

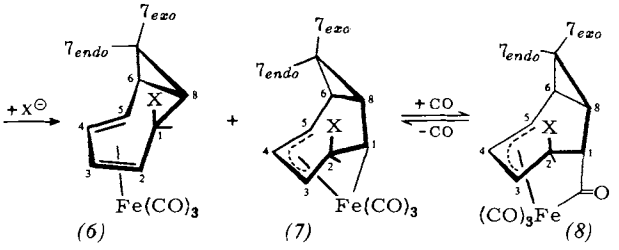
(7) *(7')* *(7')*

Since *cis,cis*-bishomobenzene *(4)* is unsuitable for synthesis of *(7)* owing to its thermal instability, this compound *(7)* was prepared by a novel route[5], namely kinetically controlled addition of H$^-$ to compound *(5)* which is easily accessible from the cyclooctatetraene-Fe(CO)$_3$ complex[4a].

(7a) is thus formed in 18% yield alongside already known *(6a)*[4a] and a little *(6c)*[4b] (total yield 90%) on treatment of *(5)* with a 3% solution of $NaBH_4$ in ice-water. With carbon monoxide, *(7a)* gives an adduct *(8a)* (m.p. 86 to 87 °C, dec.), which can be separated by fractional crystallization from pentane at −60 °C and which decomposes to regenerate *(7a)* in a vacuum (5 torr; 40 °C)[2].



(5)



(6) *(7)* *(8)*

(a), X = H; *(b)*, X = D; *(c)*, X = OH

A degenerate valence isomerization *(7)*⇌*(7')* can indeed be detected. Formally it involves migration of the cyclopropane ring from positions 6, 7, 8 to 1, 2, 3 and simultaneous shift of the π-allyl-iron bond from 3, 4, 5 to 4, 5, 6 and of the σ-carbon-iron bond from 1 to 8. The rearrangement is recognizable by deuterium-labeling of C^2[6]. Since, however, a 1:1 equilibrium *(7b)*⇌*(7b')* is rapidly established in a solution of *(7b)* at room temperature, this investigation was carried out starting with compound *(8b)* which can be isolated in pure form, since it is more stable kinetically than *(7b)*, and which is connected with *(7b)* by the equilibrium[2] *(7b)* + CO⇌*(8b)*.

In the ^{1}H-NMR spectrum of *(8b)* (Fig. 1) a slow decrease in the intensity of the resonance signal of $H^{2\,endo}$ can be observed at 40 °C simultaneously with an increase to equal extent of the remaining proton signal (*ca.* 95% deuterium) due to $H^{2\,pseudoaxial}$, while the intensity of the other signals remains unchanged. Equilibrium requires *ca.* 25 min in benzene at 40 °C.

Failure attended an attempt to demonstrate the exchange of magnetic environments of the protons 4↜5, 3↜6, 2↜7, 1↜8 by the double resonance-relaxation technique[7] because *(7a)* isomerizes to 1,3,5-cyclooctatriene-Fe(CO)$_3$[8,9] at temperatures required for this experiment.

Product analysis indicates that the addition of the C^6—C^8 bond to the 1,3,4,5-η-Fe(CO)$_3$ unit of *(7)* occurs with retention at all the carbon atoms involved. We propose the systematic symbolism $3\eta\pi_s + 1\eta\pi_s + 2\sigma_s$ for this new type of cycloaddition by analogy with the nomenclature used by *Woodward* and *Hoffmann* for pericyclic reactions[10] and by *Cotton* for organometallic compounds[11].

In this connection the degenerate valence isomerization *(6)*⇌*(6')* is also of interest. If *(6b)* (m.p. 39 °C) is heated in benzene for 15 h at 90 °C, redistribution of the deuterium between the ring positions 1 *pseudoaxial* and 7 *endo* is observed[13]. This can be interpreted in terms of a valence isomerization *(6)*⇌*(6')* which, unlike the rearrangement observed with uncomplexed bicyclo[5.1.0]-2,4-octadiene[12], proceeds with retention at C^6 and C^8.

All compounds were characterized by elemental analyses, mass, IR, and ^{1}H-NMR spectra (cf. Fig. 1; assignment by double resonance experiments). The influence of substituents X on the position of the equilibria *(6)*⇌*(6')* and *(7)*⇌*(7')* is still under investigation.

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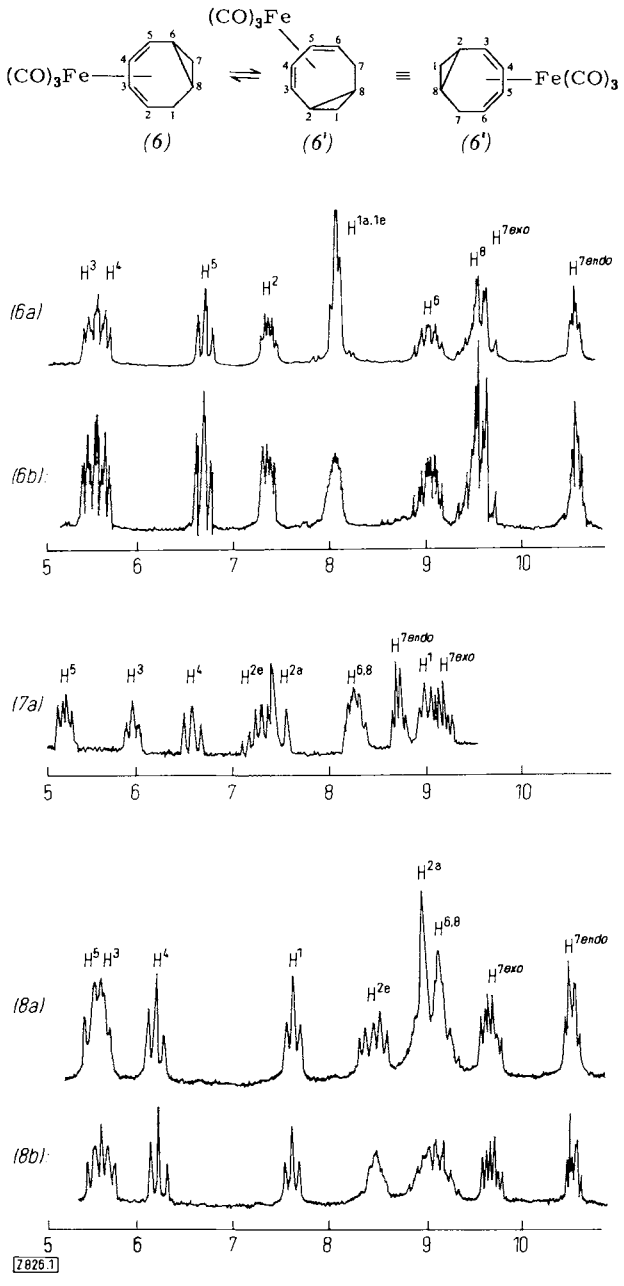

Fig. 1. ^{1}H-NMR spectra of compounds *(6)*, *(7)*, and *(8)*; all in 10% solution in C_6H_6; 100 MHz; 25 °C; internal standard TMS = 10 τ.

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1,3,5-Tri-*tert*-Butylpentalene. A Stabilized Planar 8π-Electron System[**]

By *Klaus Hafner* and *Hans Ulrich Süss*[*]

Dedicated to Professor Fritz Kröhnke on the occasion of his 70th birthday

The question of the nature of bonding in pentalene *(1)* has motivated numerous experimental and theoretical studies during the past 50 years[1] and frequently led to a great deal of controversy[2]. Whereas "aromatic" properties were initially postulated for *(1)*, recent quantum mechanical calculations predict for a delocalized pentalene according to a D_{2h} structure *(1a)* resonance destabilization by

(1a) *(1b)*

about 6 kcal/mol relative to a polyolefin structure of C_{2h} symmetry *(1b)*[3,4]. The hydrocarbon *(1)* should accordingly be characterized by high reactivity and low thermal stability. This is confirmed by the latest experimental results: attempts to prepare *(1)* and its 2-methyl, 1,3-dimethyl, and 1,3-di-*tert*-butyl derivatives exclusively yielded the dimerization products[5]. On photolysis at −196 °C[5] some of these yield the highly thermolabile monomers (detected by UV spectroscopy). Similar observations were made by *de Mayo et al.*[6] on attempted preparation of 1-methylpentalene, whose existence could likewise only be deduced from UV and IR spectra owing to its unusually pronounced tendency to undergo dimerization even at temperatures below −100 °C.

NMR spectroscopic studies of a simple pentalene were expected to provide information about the bonding character of this cyclooctatetraene perturbed by a central σ bond and thus to afford a solution of the "pentalene problem". This required a derivative of *(1)* whose dimerization is hindered by steric affects only. This requirement is fulfilled by 1,3,5-tri-*tert*-butylpentalene *(7)*.

The synthesis of *(7)* was readily accomplished by reaction of lithium *tert*-butylcyclopentadienide *(2)* with the ketimonium salt *(3)*[7] in ether/methylene chloride (2:1) at 0 °C (15 h). The reaction mixture is then rapidly worked up at 0 °C and the product mixture chromatographed on Al_2O_3 (activity 3, basic) at −75 °C with *n*-pentane. Com-

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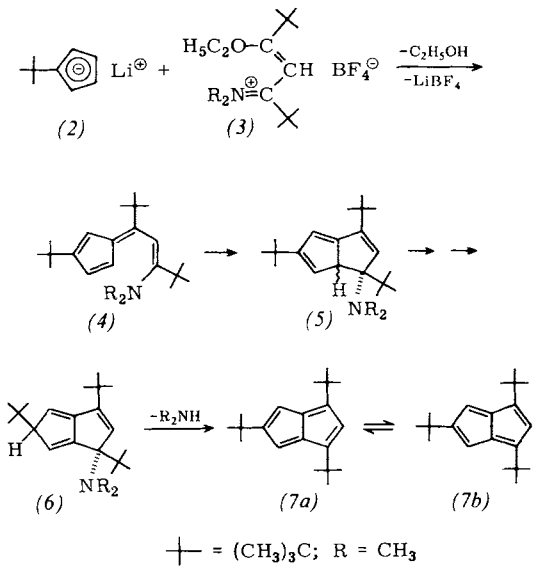

pound *(7)* is isolated in about 10% yield[9] as deep-blue crystals (scales) of m.p. 59 °C (low temperature MS (at −100 °C): $M^+ = 270$[10]). The crystals are stable for several hours at room temperature in the absence of air, while a low concentration *n*-hexane solution of the compound is stable for several days under N_2. Dimer formation has not yet been observed.

By analogy with the preparation of 2-methyl- and 1,3-dimethylpentalene[5], *(2)* and *(3)* probably first yield the fulvene *(4)* which undergoes electrocyclic reaction to give *(5)*. Subsequent double 1,5 H shifts lead to the 1,5-dihydropentalene *(6)* which suffers 1,4-elimination of dimethylamine to furnish *(7)*.

The UV spectrum of *(7)* [(in *n*-hexane at 20 °C): $\lambda_{max} = 211$ ($\log\varepsilon = 4.27$), 280 (3.34), 333 (3.50), and 598 nm (1.81)] is in good agreement with calculated[4] values for the electronic spectrum of *(1)* and resembles those of mono- and dimethylpentalenes[5,6] as well as those of hexaphenylpentalene[11], 1,3-bis(dimethylamino)pentalene[12], and 1,4-diamino-2,5-dicyano-3,6-dimethylpentalene[13].

The pentalene structure *(7)* is proved by the NMR spectra, which provide additional information about the bonding

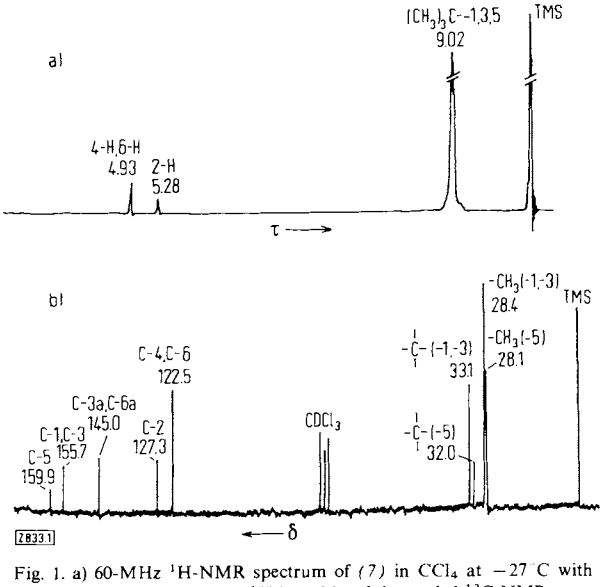

Fig. 1. a) 60-MHz ^{1}H-NMR spectrum of *(7)* in CCl_4 at −27 °C with TMS as internal standard. b) ^{1}H-broad band decoupled ^{13}C-NMR spectrum of *(7)* in $CDCl_3$ at −50 °C with TMS as internal standard.

character of the 8 π-electron system. The 60-MHz ^{1}H-NMR spectrum of *(7)* (Fig. 1a) shows two singlets of intensity 2:1 for the three ring protons, while the absorptions of the *tert*-butyl protons coincide to give just one signal. The ^{13}C-NMR spectrum of *(7)* (Fig. 1b)[14] contains five signals in the sp^2 C range for the ring system. This assignment was deduced from the off-resonance spectrum, the known influence of *tert*-butyl groups on neighboring sp^2 C atoms, as well as the relative intensities of the signals of C-1/C-3, C-5, C-3a/C-6a on the one hand and of C-2, C-4/C-6 on the other. In contrast to the 60-MHz ^{1}H-NMR spectrum, the ^{13}C-NMR spectrum permits recognition of the different *tert*-butyl groups.

The ring proton signals of *(7)* are shifted upfield compared to those of heptalene (τ = 4.2 and 4.9)[15], cyclooctatetraene (τ = 4.31)[16], and particularly those of fulvene (τ = 3.9)[17] and 1,2-dihydropentalene (τ = 3.29—4.18)[18]. The same observation is made on comparison with the signals of the outer protons of [16]annulene (τ = 4.67)[19] and of 1,7-methano[12]annulene (τ = 4.2—4.6)[20], both of which exhibit a paramagnetic ring current.

Accordingly, a paramagnetic ring current is probably operative in *(7)* too, the compound thus possessing "antiaromatic" character. The presence of only five signals in the ^{13}C-NMR spectrum for the eight ring C atoms of *(7)* rules out the existence of a localized bond system depicted by one of the Kekulé structures *(7a)* and *(7b)*. However, our present experimental results do not permit a decision whether the π-electron system of *(7)* is delocalized in the same way as *(1a)* or is undergoing rapid oscillation between the Kekulé structures *(7a)* and *(7b)*.

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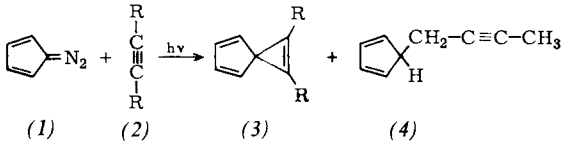
Definite Proof of Spiroconjugation in [1.2]Spirenes[**]

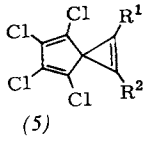
By *Heinz Dürr, Bernd Ruge*, and *Heribert Schmitz*[*]

Linkage of conjugated segments of polyenes (ribbons[1]) *via* a formally sp^3-hybridized C atom should lead to a spirene exhibiting an interaction designated as spiroconjugation[2]. HMO[2] and CNDO/2 calculations[3] on [1.2]spirene[**] predict stabilization of the HOMO by interaction between the π ribbons while the energy of the LUMO remains largely unaffected[2,3]. This should result in a hypsochromic shift of the longest wavelength UV band compared with that of the partially hydrogenated system *(7)*.

However, both electronic and steric substituent effects can perturb the system and mask the spiroconjugation. Thus the spirene *(5c)* provides no unequivocal evidence for spiroconjugation[2], whereas *(5d)* and *(5e)* exhibit a marked hypsochromic shift in the UV spectrum[4]. These differing results prompted us to synthesize the alkyl-substituted [1.2]spirenes *(3a)* and *(3b)* in order to substantially eliminate substituent effects.



(1) *(2)* *(3)* *(4)*



(5)

(a), R = CH_3 *(d)*, R^1 = H, R^2 = CO_2CH_3

(b), R = C_2H_5

(c), R^1 = R^2 = C_2H_5 *(e)*, R^1 = R^2 = CO_2CH_3

Compounds *(3a)* and *(3b)* were prepared by irradiating diazocyclopentadiene *(1)* in 2-butyne *(2a)* or 3-hexyne *(2b)* with long wave UV light (λ > 360 nm) until evolution of nitrogen had ceased (cf. ref. [5]). *(3a)* and *(3b)* are pale yellow oils (yield 47 and 35% respectively) which decompose on attempted gas chromatography but could be purified by chromatography and vacuum microdistillation at room temperature.

The structure follows from the spectra. IR: *(3a)*: 1938; *(3b)*: 1925 cm^{-1} (cyclopropene stretching mode); NMR: *(3a)*: τ = 3.8—4.0 (m) and 3.3—3.5 (m) (cyclopentadiene H), 7.86 ppm (s) (CH_3) (2:2:6); *(3b)*: τ = 3.3—3.5 (m) and 3.7—3.9 (m) (cyclopentadiene H), 7.53 (q) (^3J = 7.5 Hz) (CH_2) and 8.95 ppm (t) (CH_3) (2:2:4:6); mass spectrum: *(3b)*: *m/e* = 146 (M^+); UV, see Table 1. Further structural proof comes from the Diels-Alder adducts of *(3a)* and *(3b)* to tetracyanoethylene and to 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (cyclopropene band at 1860 to 1880 cm^{-1}).

(6) *(7)* *(8)*

Table 1. UV data for [1.2]spirenes *(3a)* and *(3b)* and the 5,5-disubstituted cyclopentadienes *(6)*—*(8)*.

Cpd.	Solvent	λ_{max} [nm]	ε
(3a)	methanol	239	1300
(3b)	methanol	241	2450
	isooctane	242	2900
(6)	ethanol	250	2880
(7)	ethanol	257	2690
(8)	ethanol	254	2750

The possibility of spiroconjugation was examined by comparison of the UV spectra of *(3a)* and *(3b)* with those of *(6)*—*(8)* which cannot show spiroconjugation. The theoretically predicted hypsochromic shift[2,3] of the longest wavelength absorption band is indeed observed on comparison of *(3a)* and *(3b)* with *(8)*. It amounts to 12—15 nm, *i.e.* 5—6 kcal/mol.

While the UV spectra of spirotetraenes may be compared with those of the corresponding saturated hydrocarbons[6,7], the method runs into difficulties with *(3a)*, *(3b)*, and *(7)*. The p orbitals (Walsh model) of the cyclopropene single bonds can enter into pseudoconjugation *via* the sp^2-hybridized spiro-C atom with the π electrons of the five-membered ring[8]. In *(3a)* and *(3b)* a hypsochromic shift becomes operative due to spiroconjugation and a bathochromic shift due to pseudoconjugation. Comparison of *(7)* and *(8)* shows that the latter effect should result in a bathochromic shift of the order of 3 nm. In reality the stabilization of *(3a)* and *(3b)* will therefore be greater than 5—6 kcal/mol. Spiroconjugation can thus be regarded as established in [1.2]spirenes. Photoelectron spectroscopic studies are currently in progress.

1,2-Diethylspiro[2.4]hepta-1,4,6-triene (3b):

A solution of *(1)* (4.0 g, 43.5 mmol) in *(2b)* (150 ml) was irradiated, after 15 minutes' purging with N_2, with a Philips HPK 125 W lamp (GW_v filter) for 4 h at 0 °C. (60—70% of the calculated amount of N_2 was liberated.) Unreacted *(2b)* was then removed *in vacuo* and the blackish brown residue rapidly chromatographed over silica gel (150 g) with CH_2Cl_2. Chromatography with CCl_4 under the same conditions afforded *(3b)* as a pale yellowish oil. Prior to spectroscopy *(3b)* was distilled in a microapparatus at room temperature.

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Mesomolecules. Polyaza-Polyoxa Macropolycyclic Systems[**]

By *Jean-Marie Lehn, Jacques Simon*, and *Joseph Wagner*[*]

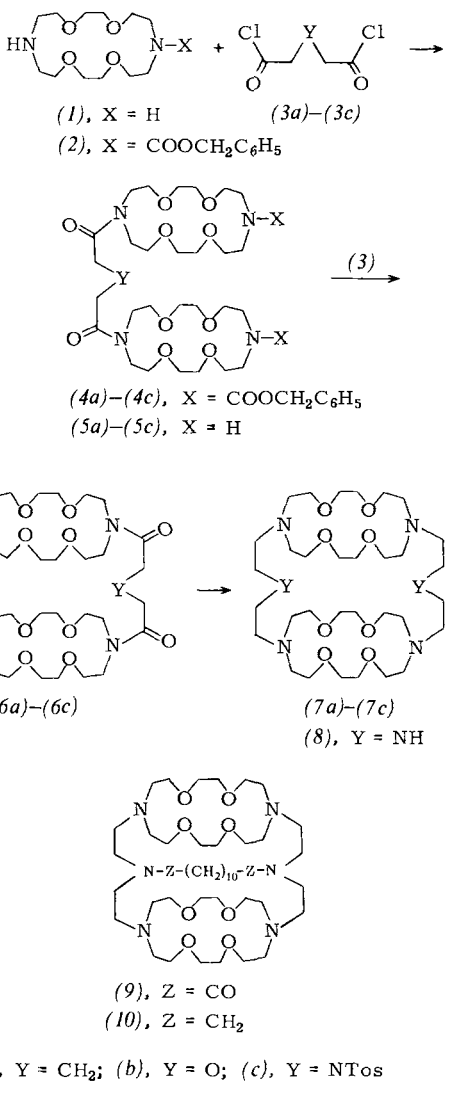
The chemistry of molecular systems presents quite a clear dichotomic separation into the micromolecules of organic chemistry (M.W. < 500) and the macromolecules of polymer chemistry and biochemistry (M.W. > 5000). Although these definitions of size are arbitrary, it nevertheless appears that comparatively very few organic chemical studies have been directed towards the design, the synthesis, and the properties of molecules of intermediate size, *i.e.* mesomolecules (not considering systems akin to natural products like porphyrins, corrins, peptides, *etc.*).

Such systems may present a multitude of new properties compared to "small" molecules, by the mere token of their size and the resulting palette of possible structural variations, while also being challenging synthetic targets. A number of macrocyclic[1], macrobicyclic[2-4], and macrotricyclic[5,6] molecules have been synthesized recently. Many of them may act as ligands for the formation of selective inclusion complexes[1,3,4,6-8] ("cryptates")[7] with various metal cations; natural macrocyclic peptides and depsipeptides also form cation complexes[9]; macrocyclic polysugars, the cyclodextrins, are able to form molecular inclusion complexes[10]. The common feature of these systems, which are still of relatively small size, is the presence of a molecular cavity which confers upon them their specific properties.

We present here the synthesis of several macrotricyclic and macrotetracyclic molecules. The intramolecular cavity of these systems is appreciably larger than in the previously reported cation ligands[1,3,4,6]; thus, in addition to new conformational and cation complexation properties, they might be able to complex molecules, *i.e.* to function as specific molecular receptors[14].

Monoprotection of the macrocyclic diamine *(1)*[3a] using benzyl chloroformate in benzene (diamine: chloroformate = 1:1) gives compound *(2)* (viscous oil) in 50% yield[12]. Condensation of *(2)* with the diacyl dichlorides *(3a)*, *(3b)*[11], and *(3c)* (m.p. 92 °C) affords respectively the diamides *(4a)*, *(4b)*, and *(4c)*, which are then converted into *(5a)*, *(5b)*, and *(5c)* with hydrogen bromide in acetic acid (48%). Products *(4)* and *(5)* have not yet been obtained in a crystalline form; the yields are about 90% for the two steps.

The next step is performed under high dilution conditions following a procedure very similar to the one used for the synthesis of the previously described macrobicyclic systems[3]. Condensation of *(5a)*, *(5b)*, and *(5c)* with the dichlorides *(3a)*, *(3b)*, and *(3c)* respectively (in benzene and in the presence of three equivalents of triethylamine) affords the macrotricyclic tetracarboxamides *(6a)* (m.p. 185—186 °C; yield 75%), *(6b)* (m.p. 185 °C; yield 70%), and *6c)* (m.p. 223 °C; yield 55%). These tetraamides *(6)* are reduced by diborane in tetrahydrofuran[13] (reflux for about 10 hours). Hydrolysis of the resulting products with 6N HCl (reflux for about 10 h) followed by passage



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of the aqueous solutions over a quaternary ammonium resin column in its hydroxide form affords the macrotricyclic tetraamines *(7a)* (m.p. 45—46 °C; yield 90%), *(7b)* (m.p. 64 °C; yield 90%), and *(7c)* (m.p. 152 °C; yield 90%).

Removal of the tosyl groups of *(7c)* by treatment with sodium in liquid ammonia/ethylamine (1:1) gives *(8)* (m.p. 92—94 °C; yield 70%). The hexaamine *(8)* is then condensed under high dilution conditions with dodecanedioyl dichloride to give the macrotetracyclic diamide *(9)* (viscous oil; 40%). Reduction with diborane followed by acid hydrolysis and passage over a basic resin column, following the procedure used above for the *(6)*→*(7)* conversion, leads to the macrotetracyclic diamine *(10)* (viscous oil; yield 95 %).

The analytical and spectral (^{1}H-NMR, mass) data for all compounds were in agreement with the proposed structures *(1)*—*(10)*. The ^{13}C-NMR spectra of *(6b)* and *(6c)* are also in agreement with these structures. The tri- and tetracyclic substances *(6)*—*(10)* are all soluble in water except *(6c)* and *(7a)* (slightly soluble), as well as in most organic solvents.

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Molecular and Cation Complexes of Macrotricyclic and Macrotetracyclic Ligands[**]

By *Jean-Marie Lehn*, *Jacques Simon*, and *Joseph Wagner*[*]

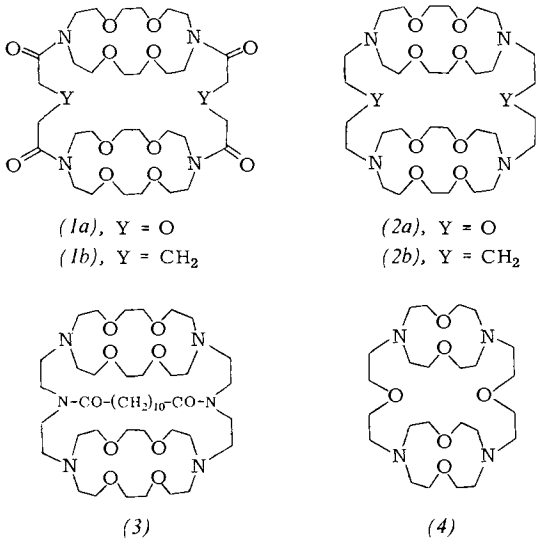
The molecular recognition process involved in the association of two or more chemical species to form a complex is controlled by the chemical information stored in the ligand[1]. The control of spherical recognition of alkali cations[1] by synthetic macrocyclic[2], macrobicyclic[3], and macrotricyclic[4] ligands forming inclusion complexes has been the subject of a number of recent studies.

Beyond the spherical substrate (alkali cations), the next step resides in the design of synthetic ligands for organic molecules, *i.e.* of synthetic molecular receptors. In addition to being selective, such complexes might also in principle display highly specific functions. For instance, they may act as protoenzymes or induce the transport of molecules through various "membrane" type barriers.

Substances capable of functioning as receptors for molecules should contain a molecular cavity so as to be able to form inclusion complexes. Up to now one kind of compound, the macrocyclic polysugars, cyclodextrins[5], has been shown to form well defined inclusion complexes with various molecular substrates[5-7]. Occlusion of solvent molecules by macrocyclic molecules has also been reported[8].

We present here a report on the complexation properties displayed by the macrotricyclic and macrotetracyclic molecules[9]. Three types of complexes have been observed and we now describe the nature and the qualitative properties of these species.

First, the formation of *metal cation complexes* has been observed as in the case of the previously described substance *(4)*[4]. A chloroform solution of *(2a)* turns yellow when solid sodium, potassium, or cesium picrate is added,



owing to the dissolution of the salt by complexation of the cation. It is probable that complexes of both 1:1 and 2:1 cation/ligand stoichiometries may be obtained. A complex [*(2a)*, 2NaI] has been isolated and characterized. The formation of 1:1 and 2:1 complexes with several alkali cations has been detected for compounds *(2a)* and *(2b)* using cation selective electrodes. In analogy with the results obtained for compound *(4)*, these cation complexes may be formulated as 1:1 and 2:1 inclusion complexes of the [3]-cryptate type[4].

Second, *lipophilic cation/lipophilic anion association* occurs when salts containing a complexable cation and a lipophilic anion are used. The fluorescence of the fluorescent probe 6-*p*-toluidinonaphthalene-2-sulfonate (TNS) is known to increase markedly when the anion complexes with a lipophilic substrate[10, 11]. In the present case, complexation of an alkali cation in aqueous solution by the ligand *(2a)* gives a lipophilic cation. The TNS anion may then associate with the cation complex, forming a lipophilic cation/lipophilic anion pair. Such an association should lead to a strong increase in TNS fluorescence. This is indeed observed for ligand *(2a)* with the TNS potassium salt, but no special effect is found for the other alkali cations (Fig. 1). Thus, K^+ probably forms a quite stable complex with *(2a)* and the resulting [*(2a)*, K^+] species associates with the anion forming a neutral pair {[*(2a)*, K^+], TNS^-}.

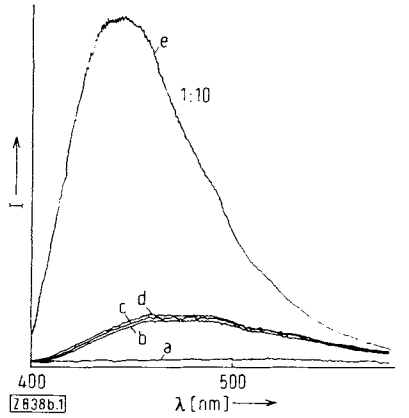


Fig. 1. Fluorescence spectra of the TNS^- anion a) $N(C_2H_5)_4^+$ TNS^-; b) $N(C_2H_5)_4^+$ TNS^- + *(2a)*; $N(C_2H_5)_4^+$ TNS^- + *(2a)* + LiI: $N(C_2H_5)_4^+$ TNS^- + *(2a)* + CsI; c) $N(C_2H_5)_4^+$ TNS^- + *(2a)* + NaI; d) $N(C_2H_5)_4^+$ + *(2a)* + RbI; e) $N(C_2H_5)_4^+$ + *(2a)* + KI (scale reduced by a factor of 10 for e). Solvent: water; concentrations: $N(C_2H_5)_4^+$ TNS^-: 10^{-3} mol/l; *(2a)*: 10^{-2} mol/l; salt: 10^{-2} mol/l.

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[**] Molecular Receptors, Part 2.—Part 1: ref. [9].

These results have been checked with a previously described macrobicyclic ligand for which TNS fluorescence enhancement occurs in the presence of a cation forming a complex stable in water[3]. The phenomenon has also been observed recently with natural ligands (*e.g.* valinomycin) in water[12] or in membranes[13].

Finally, *molecular complexes* have also been detected. Indeed, in the absence of any complexable cation, notable TNS fluorescence enhancements are still observed in the presence of ligands *(1)*—*(3)* (Fig. 2). This may be attributed to the formation of molecular complexes between the lipophilic TNS substrate and the ligand. Figure 2 shows that the fluorescence intensity increases with the ligand lipophilicity and is higher for a given amide *(1)* than for the corresponding amine *(2)*. Furthermore, by far the most intense fluorescence is found in the case of the macrotetracyclic ligand *(3)*, for which molecular models clearly display a hollow shape with a well defined intramolecular cavity. Fluorescence enhancements have been described in the case of cyclodextrin inclusion complexes[6, 14].

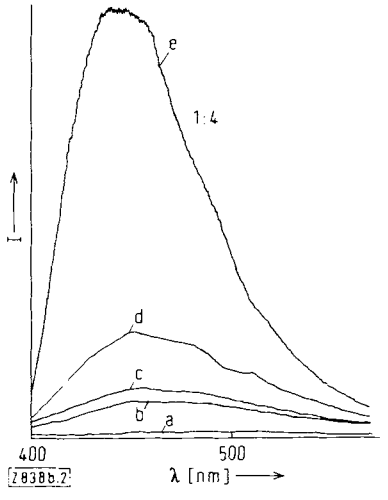

Fig. 2. Fluorescence spectra of the TNS^- anion (cation $N(C_2H_5)_4^+$, 10^{-3} mol/l) in the presence of the following ligands (10^{-2} mol/l) a) none; b) *(2a)*; c) *(1a)*; d) *(1b)*; e) *(3)* (scale reduced by a factor of 4 for e). Solvent: water.

It is tempting to propose that the molecular complexes formed by the present synthetic ligands are also of the inclusion type. However, the present results do not yet permit distinction between an external addition complex and an inclusion complex. Nevertheless, the ligands *(1)*—*(3)* do indeed function as molecular receptors.

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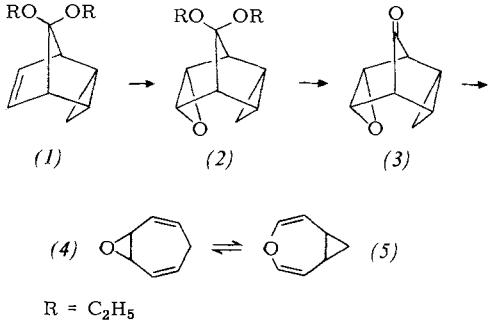
Rapid Reversible Cope Rearrangement between the *sym*-Oxabicyclo[5.1.0]octa-2,5-dienes

By *Helmut Klein, Wilhelm Kursawa*, and *Wolfram Grimme*[*]

The rapid reversible Cope rearrangement of bicyclo[5.1.0]-octa-2,5-diene (also known as 3,4-homotropilidene)[1] was spectacularly extended to bullvalene[2] and semibullvalene[3], but so far has been limited to carbocycles[4]. In the present communication we describe the *sym*-oxabicyclo-[5.1.0]octa-2,5-dienes *(4)* and *(5)*, a pair of heterocycles in mutual equilibrium *via* a rapid Cope rearrangement.



The Diels-Alder adduct *(1)*[5] of 5,5-diethoxycyclopentadiene and cyclopropene can be converted by *m*-chloroperbenzoic acid in methylene chloride into the liquid epoxide *(2)* which is hydrolyzed by 70% aqueous acetic acid to the epoxy ketone *(3)* [81%; m. p. 129 °C; NMR ($CDCl_3$, TMS internal): $\tau = 6.82$ (t) (epoxide H), 7.20 (sex) (bridgehead H), 8.82 ppm (m) (cyclopropane H); IR (KBr): $\nu_{C=O} = 1768\ cm^{-1}$]. We deduce the epoxy ring to be *endo* from the deshielding of one of the secondary cyclopropane protons in *(2)* and *(3)* relative to those in hydrogenated *(1)* and the corresponding ketone, as well as from the coupling constant of 1.5 Hz between the epoxide and bridgehead protons[6].

Sublimation of the ketone *(3)* through a capillary heated to 380 °C (45 cm, 0.3 cm diam.) in a stream of N_2 induced fragmentation to CO and 8-oxabicyclo[5.1.0]octa-2,5-diene *(4)* (92%) obtained crystalline at −70 °C. The structure of the new heterocycle, which is liquid at room temperature, follows from the spectral data. The UV spectrum [(cyclohexane): $\lambda_{max} = 280$ ($\varepsilon = 600$), $\lambda_{min} = 258$ nm (450)] exhibits extensive end absorption and its shape resembles that recorded for 2,6-dimethyloxepin[7]. As in the case of 3,4-homotropilidene, the IR spectrum displays an intense band at 1664 cm^{-1}, accompanied by a characteristic band at 1138 cm^{-1} due to the epoxide ring.

However, the most convincing structural evidence comes from variable temperature NMR spectra (Fig. 1). The

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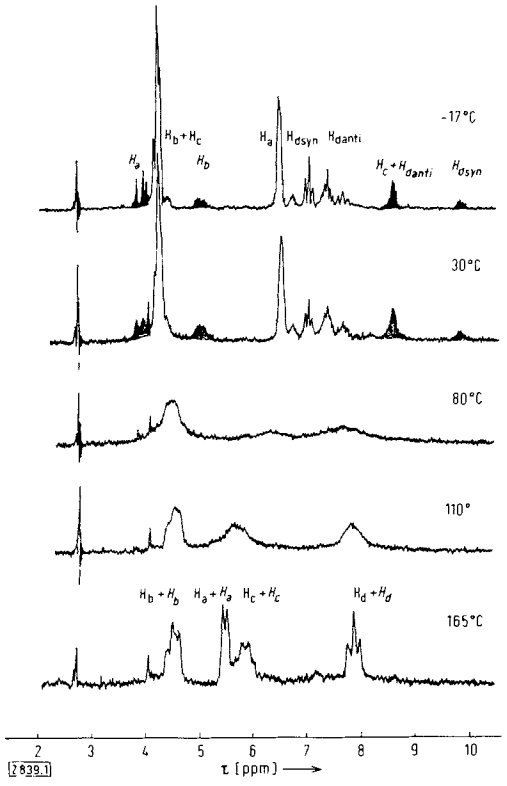
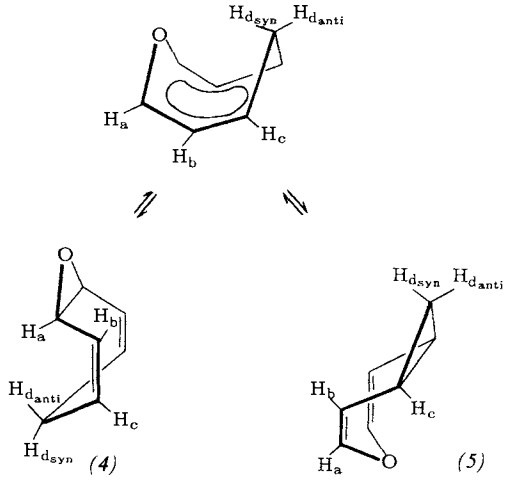


Fig. 1. ^{1}H-NMR spectrum of the equilibrium of *sym*-oxabicyclo[5.1.0]-octa-2,5-dienes at various temperatures [60 MHz, *sym*-tetrachlorodideuterioethane, $CHCl_3$ ($\tau = 2.75$) as internal standard]. The residual ^{1}H of the solvent absorbs at $\tau = 4.06$. The signals of the epoxytropilidene *(4)* are listed in regular type, those of the homooxepin *(5)* in italics, they are also shaded.

spectrum at -17 °C is dominated by two narrow multiplets at $\tau = 4.30$ and 6.50 and by a split AB system at 6.90 and 7.55 ppm ($J_{A,B} = 17$ Hz) ascribable to the protons indicated in the 3,4-epoxytropilidene *(4)*. In addition, there appear a low intensity AB system with a split B part at $\tau = 3.95$ and 5.10 ($J_{A,B} = 7.5$ Hz) and two multiplets at 8.60 and 9.85 ppm. These signals arise from the protons of the valence isomer 4,5-homooxepin *(5)* present in small amount. At about 30 °C the signals become diffuse, indicating an equilibrium between *(4)* and *(5)* that is just becoming dynamic on the NMR time scale. Further increase in temperature leads *via* coalescence to the appearance of four new signals exhibiting fine structure at 165 °C. This reversible temperature dependence of the spectrum results from the increasing rate of equilibration $(4) \rightleftarrows (5)$ causing the absorption of the interconverting protons to be recorded at an average value. The methylene protons H_d, showing separate absorptions in each of the two equilibrating species corresponding to their *syn* and *anti* configuration, can only be equivalent in the high temperature spectrum when their two average values coincide. This is the case when the more strongly shielded methylene proton ($\tau = 9.85$) of the cyclopropane ring exchanges with the less shielded one ($\tau = 6.90$) of the seven-membered ring and the other two methylene protons interconvert correspondingly.

The coupling constants ^3J and ^4J[8] of the bridgehead and methylene protons reveal that both equilibrium components are in the transoid conformation and that the exchange pattern mentioned above, which has been confirmed by double resonance, interrelates the *syn* and the *anti* methylene protons of *(4)* and *(5)* respectively. This would indicate the cisoid conformation for the transition state in analogy to the 3,4-homotropilidene rearrangement[9].



The equilibrium constant $K = [(4)]:[(5)]$ is found to be 6.45 and 4.12 for -17 and 30 °C, respectively, by integration of the NMR spectra; the position of the averaged signals at 165 °C affords a value of 1.67. The transition $(5) \rightarrow (4)$ is thus characterized by $\Delta\Delta H_f^0 = -1.67 \pm 0.33$ kcal/mol and $\Delta S^0 = -4.4 \pm 1.0$ cal mol^{-1}deg^{-1}. The free energy of activation for the rearrangement can be roughly estimated as $\Delta F^{\neq} = 17$ kcal/mol from the coalescence spectrum[10].

The dynamic equilibrium at room temperature between epoxytropilidene and homooxepin corresponds to the "fluxional structure" of 3,4-homotropilidene[1] and impressively confirms for an intramolecular case our previous finding[11] that the activation energies for the Cope rearrangements of *cis*-divinyl-substituted three-membered rings lie closer together than formerly assumed.

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Polynuclear π-Cyclopentadienyl-Sulfur-Molybdenum Complexes from Propylene Sulfide and π-Cyclopentadienylcarbonylmolybdenum Hydrides[1]

By *Wolfgang Beck*, *Wolfgang Danzer*, and *Gerhard Thiel*[*]

The reaction of hydridopentacarbonylmanganese with propylene sulfide proceeds *via* insertion of sulfur into the Mn—H bond to give the dimeric SH-bridged complex $[Mn(CO)_4SH]_2$[2]. In other reactions with metal hydrides too, 2-methylthiirane proves to be a simple reagent for introduction of sulfur atoms into metal complexes under mild conditions[3].

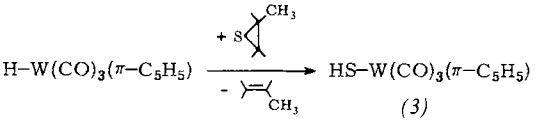
Thus $HMo(CO)_2[P(OC_6H_5)_3]$ (π-C_5H_5) and propylene sulfide (molar ratio 1:1) in tetrahydrofuran at 20 °C yield lustrous black, oxygen-sensitive crystals of (π-$C_5H_5)_3Mo_3S_4$ *(1)*. The mass spectrum of *(1)* contains the series of ions $(C_5H_5)_{3-n}Mo_3S_4^+$ and $(C_5H_5)_{3-n}Mo_3S_3^+$ ($n=0$—3), as well as $(C_5H_5)_{3-n}Mo_3S_4^{2+}$ and $(C_5H_5)_{3-n}Mo_3S_3^{2+}$ ($n=0,1$); the stability of the Mo_3S_3 unit warrants attention. The structure of the diamagnetic cation $(\pi\text{-}C_5H_5)_3Mo_3S_4^+$ is known[4]; a three-membered Mo_3 ring is also assumed for the neutral molecule *(1)*, the compound *(1)* being predicted to have a smaller Mo—Mo distance than in the cation by the MO model of *Dahl*[4].

If $HMo(CO)_2[P(OC_6H_5)_3]$ (π-C_5H_5) is allowed to react under similar conditions with an excess of propylene sulfide, black crystals of the dinuclear complex $(\pi\text{-}C_5H_5)_2Mo_2S_4$ *(2a)* are formed. A red isomer $(\pi\text{-}C_5H_5)_2Mo_2S_4$ *(2b)* which is more readily soluble in methylene chloride is formed from $HMo(CO)_3(\pi\text{-}C_5H_5)$ and propylene sulfide. The mass spectra of *(2a)* and *(2b)* contain the ions $(C_5H_5)_2Mo_2S_n^+$ ($n=4$—0), $C_5H_5Mo_2S_n^+$ ($n=3,1$), $Mo_2S_n^+$ ($n=4,3$), and $(C_5H_5)_2Mo_2S_n^{2+}$ ($n=4$—2). *(2a)* differs from *(2b)* in the additional appearance of a metastable peak arising from the fragmentation

$$(C_5H_5)_2Mo_2S_4^+ \rightarrow (C_5H_5)_2Mo_2S_2^+ + S_2$$

and above all in an additional intense IR band at 482 cm^{-1} (νS—S?). These findings indicate a structure with two disulfide bridges for *(2a)*. The structure of an isoelectronic complex $(\pi\text{-}C_5H_5)Mo(SCH_3)_4Mo(\pi\text{-}C_5H_5)$ has already been established by *Dahl*[5]. A structure analogous to the oxo compound $(\pi\text{-}C_5H_5)(O)MoS_2Mo(O)(\pi\text{-}C_5H_5)$[6] seems plausible for *(2b)*.

The reaction of $HW(CO)_3(\pi\text{-}C_5H_5)$ with propylene sulfide proceeds without displacement of carbon monoxide:



(3)

The IR spectrum of the product *(3)* exhibits two νCO bands at 2028 and 1937 cm^{-1} (in CS_2); the SH proton appears at τ 12.79 in the ^{1}H-NMR spectrum (solution in CS_2)[7].

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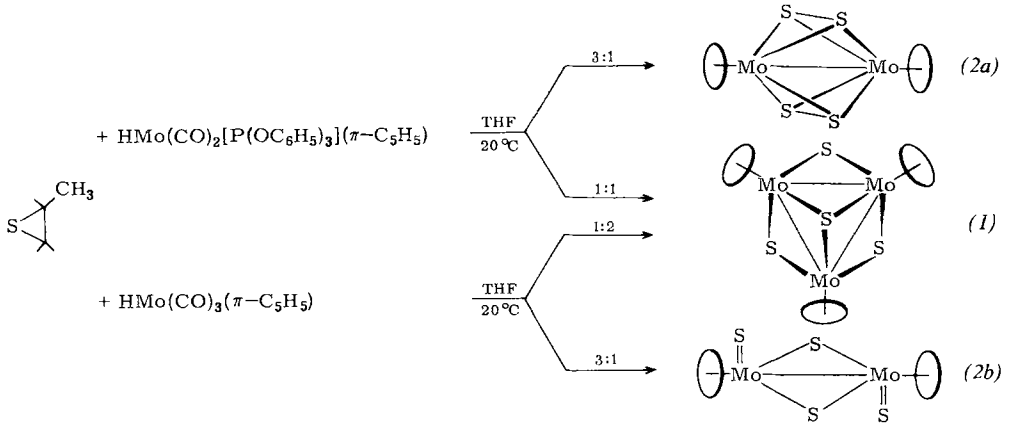
[7] We are grateful to Dr. *H. Vahrenkamp* for valuable discussions. The structures of compounds *(1)*, *(2a)*, and *(2b)* are the object of current X-ray studies by *W. P. Fehlhammer* and *A. Liu*.

Tetravalent Copper: $Cs_2[CuF_6]$[1]

By *Werner Harnischmacher* and *Rudolf Hoppe*[*]

After numerous unsuccessful attempts[2] we have finally obtained the first known compound of copper(IV), *viz.* cesium hexafluorocuprate(IV) as a beautiful orange-red solid which undergoes vigorous decomposition with water. Preparation was by *high-pressure fluorination* (Monel autoclave; 3d, 410 °C, 350 atm of F_2) of prefluorinated



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mixtures of $CsCuCl_3$ and CsCl (1:1, p.a. grade chemicals *ex* Merck; 15h, 370 °C, F_2 stream).

Guinier diagrams according to *Simon*[3] contain no Cs_3CuF_6 reflections and confirm the splitting of the $K_2[PCl_6]$-type reflection pattern ("*a*" ≈ 8.7 Å) which is probably due to the Jahn-Teller effect expected for the low spin d^7 configuration.

Preliminary measurements show $Cs_2[CuF_6]$ (F: exp. 25.5, 25.8%; calc. for Cs_2CuF_6: 25.71, for Cs_2CuF_5: 22.39%) to be *paramagnetic* and practically ($\Theta = -3$ K) to obey the Curie law (3.2—294 K). As for $Cs_2K[AgF_6]$[4] the observed magnetic moment $\mu = 1.5_5$ μ_B lies well below the expected value (1.73 μ_B, spin only). The presence of Cu^{III} is thus ruled out. The reason for the low moment is not yet known for either compound.

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Proof of the Chirality of Rapidly Interconverting Enantiomers[**]

By *Albrecht Mannschreck*, *Violet Jonas*, and *Bernd Kolb*[*]

A few years ago *Pirkle*[1] described a new method for the determination of enantiomeric purity. This method is based on the possibility of observing different NMR spectra for enantiomers when they undergo a sufficiently strong enough interaction in solution with an optically active auxiliary compound[2]. To explain this effect, it is assumed that two diastereomeric association complexes are formed which are in equilibrium with the unassociated components.

Most of the previous observations of diastereomeric association complexes are related to enantiomers which cannot interconvert thermally, namely chiral molecules with tetravalent C, P, or N atoms. In some cases enantiomers were investigated whose rates of interconversion are very low at room temperature, for example, a number of sulfoxides[2-4] and sulfinic acid derivatives[2], allenes[5], as well as *trans*-diaziridines. Recently we were able to prove the chirality of the latter class of compounds[6] using this method[7]. Here we report our results for diastereomeric association complexes of enantiomers which interconvert *rapidly* at room temperature[8].

The barriers to N^1 inversion are known for 1,2-diazetidinones[9], *e.g.*, $\Delta G_c^{\ddagger} = 17.0 \pm 0.2$ kcal/mol at 48 °C for *(1)*[10] (Fig. 1) in $CDBr_3$. At lower temperatures *(1)* shows separate signals for the diastereotopic methyl groups Me^1 and Me^2 and for the N^2-methylene protons H_A and H_B ($J = 15.5$ Hz). The existence of the enantiomers, *(R)-(1)* and *(S)-(1)*, is demonstrated by the observation that some of the ^{1}H-NMR signals split when optically active O^2, O^3-dibenzoyltartaric acid, *e.g.* (+)-*(2)*, is added. This occurs for Me^1 ($\delta = 1.15$ and 1.23), Me^2 (1.40 and 1.43), and H_B (3.60, $J = 15.5$ Hz, and 3.71, $J = 15.5$ Hz) at −55 °C (Fig. 1a). These splittings do not appear in the presence of the racemic auxiliary compound (±)-*(2)* (Fig. 1b), as is to be expected because of rapid exchange[2] of the components of a diastereomeric association complex.

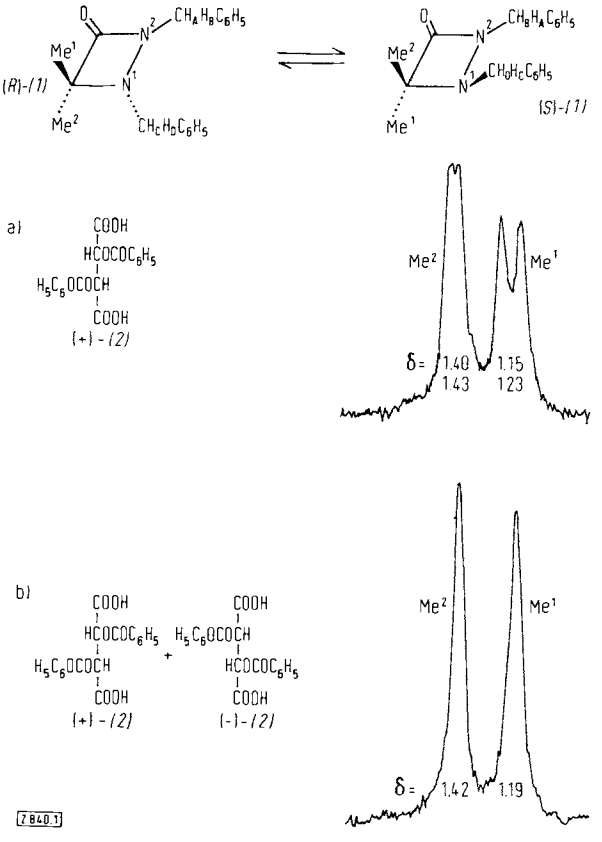

Fig. 1. ^{1}H-NMR signals of the methyl groups of (*RS*)-4,4-dimethyl-N^1,N^2-dibenzyl-1,2-diazetidinone, (*RS*)-*(1)*, in $CDCl_3$ at −55 °C and 100 MHz in the presence of an equimolar amount a) of (2*R*, 3*R*)-O^2, O^3-dibenzoyltartaric acid, (+)-*(2)*, or b) of the corresponding (2*RS*, 3*RS*)-acid, (±)-*(2)*, as auxiliary compound.

Details about the barriers to *N*-aryl rotation have been given for appropriately 2,6-disubstituted aniline derivatives[11], *e.g.*, $\Delta G_c^{\ddagger} = 16.5 \pm 0.3$ kcal/mol at 70 °C for *(3)* and >20 kcal/mol at >127 °C for *(4)* (Fig. 2) in C_4Cl_6. The rather high barrier to rotation about the partial N—N double bond leads to the (*E*)/(*Z*) isomeric nitrosamines *(3)* and *(4)*. They can be separated[12, 14] and equilibrate at a measurable rate at 29 °C in CCl_4, with formation of an equilibrium mixture of 58% *(3)* and 42% *(4)*[11, 13] which was used for the measurements described below. Due to hindered *N*-aryl rotation in *(3)* and *(4)*, separate NMR signals are observed at 10 °C for the diastereotopic methylene protons H_A and H_B ($J = 14.0$ Hz) and H_C and H_D ($J = 14.1$ Hz). The enantiomers *(R)-(3)*, *(S)-(3)*, *(R)-(4)*, and *(S)-(4)* (Fig. 2) can be detected by adding optically active 2,2,2-trifluoro-1-phenylethanol, *e.g.*, (+)-*(5)*, which causes most of the signals to split (Fig. 2a). As expected, these splittings do not appear in the presence of racemic auxiliary compound (±)-*(5)* (Fig. 2b).

The chirality of enantiomers in unresolved racemic mixtures cannot be proved with chiroptical methods. However, in favorable cases this can be achieved indirectly by the observation of diastereotopic atoms within a molecule by NMR spectroscopy, as was originally done in the cases of *(1)*[9], *(3)*[11], and *(4)*[11]. The procedure described

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[**] Application of NMR Spectroscopy of Chiral Associates, Part 1. This work was supported by the Fonds der Chemischen Industrie. Prof. Dr. *G. Snatzke*, Bochum, gave us some helpful information.

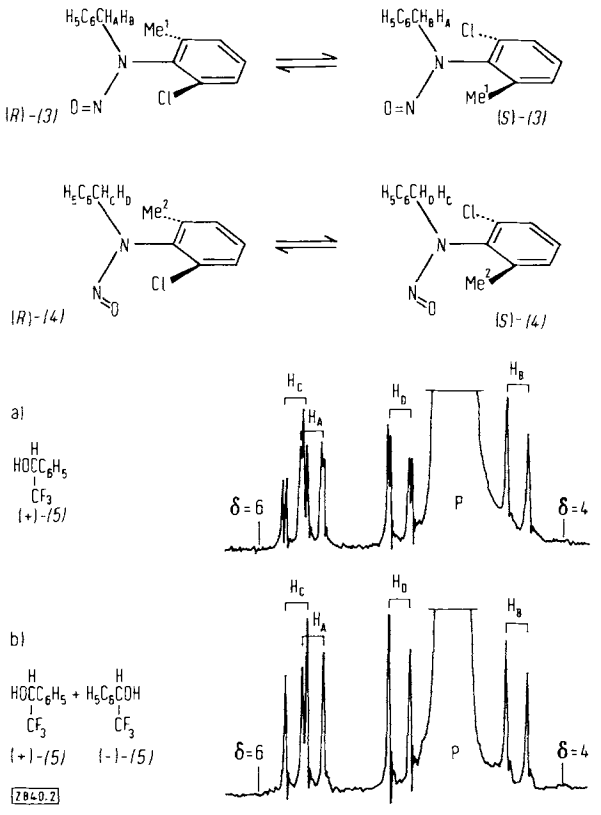

Fig. 2. ^{1}H-NMR signals of the methylene groups of (*E*)-(*RS*)-(2-chloro-6-methylphenyl)benzylnitrosamine, (*RS*)-*(3)*, and of the (*Z*) isomer, (*RS*)-*(4)*, in CCl_4 at 10°C and 100 MHz in the presence of a six-fold molar amount a) of (*S*)-2,2,2-trifluoro-1-phenylethanol, (+)-*(5)*, or b) of the corresponding (*RS*)-alcohol, (±)-*(5)*, as auxiliary compound. P: OCH and OH absorptions of *(5)*. δ and *J* values see Table 1.

The chemical shift differences Δδ (Table 1) for the matching protons appearing in the presence of the optically active auxiliary compounds decrease with increasing temperature[2] since this causes the association equilibria to shift towards the free components. The presently investigated enantiomers interconvert rapidly, so that, in addition, there is the possibility of a coalescence of the signals of the matching protons which is brought about kinetically. The successful detection[16] of such coalescences offers a new method of determining the interconversion rates of enantiomers.

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Table 1. ^{1}H-NMR chemical shifts δ (in ppm *vs.* TMS; increasing positive numbers indicate decreasing field strength) of enantiomeric mixtures in the presence of *racemic* auxiliary compounds, as well as chemical shift differences Δδ (italicized numbers) for matching protons, which appear in the presence of *optically active* auxiliary compounds [a].

	Aux. comp.; solvent [b]	*T* [°C]	H_A	H_B	H_C	H_D	Me^1	Me^2
	(2)		4.57	3.66	~3.91	~3.87	1.19	1.42
(R)-*(1)* ⇌ *(S)*-*(1)*	$CDCl_3$	−55	*0.00*	*0.110*	*0.0*	*0.0*	*0.075*	*0.027*
			J = 15.5 Hz	*J* = 15.5 Hz	*J* = 14.5 Hz	*J* = 14.5 Hz		
	(5)		5.64	4.31			1.57	
(R)-*(3)* ⇌ *(S)*-*(3)*	CCl_4	+10	*0.014*	*0.00*	—	—	*0.022*	—
			J = 14.0 Hz	*J* = 14.0 Hz				
	(5)				5.75	5.08		1.24
(R)-*(4)* ⇌ *(S)*-*(4)*	CCl_4	+10	—	—	*0.028*	*0.015*	—	*0.00*
					J = 14.1 Hz	*J* = 14.1 Hz		

[a] The assignments in the absence of auxiliary compounds were determined from the changes in the δ values obtained upon adding benzene or tris[1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionato]europium(III), as well as by comparison with other spectra.

[b] Concentrations: 0.12 mol-% diazetidinone *(1)* and 0.12 mol-% auxiliary compound *(2)*; 6.3 mol-% nitrosamine, *i.e.*, the sum of *(3)* and *(4)*, and 37.5 mol-% auxiliary compound *(5)*.

in the present paper proves the chirality of these compounds without the application of diastereotopic atoms within a molecule and should also be successful in the case of enantiomers where such atoms are absent. The prerequisite, however, is a sufficiently strong interaction with the optically active auxiliary compound, *e.g.*, by way of hydrogen bonds[15].

[1] *M. Kainosho, K. Ajisaka, W. H. Pirkle*, and *S. D. Beare*, J. Amer. Chem. Soc. *94*, 5924 (1972), and earlier papers by *W. H. Pirkle et al.*

[2] Review: *A. Ejchart* and *J. Jurczak*, Wiad. Chem. *24*, 857 (1970); Chem. Abstr. *74*, 87004d (1971).

[3] *G. M. Whitesides* and *D. W. Lewis*, J. Amer. Chem. Soc. *93*, 5914 (1971).

[4] *R. R. Fraser, M. A. Petit*, and *J. K. Saunders*, Chem. Commun. *1971*, 1450.

[5] *F. Lefèvre, M. L. Martin*, and *M. L. Capman*, C. R. Acad. Sci., Ser. C, *275*, 1387 (1972).

[6] *A. Mannschreck* and *W. Seitz*, Angew. Chem. *81*, 224 (1969); Angew. Chem. internat. Edit. *8*, 212 (1969).

[7] *A. Mannschreck* and *W. Seitz* in: IUPAC: XXIIIrd Int. Congr. Pure Appl. Chem., Vol. 2, p. 309. Butterworths, London 1971; *W. Seitz*, Dissertation, Universität Heidelberg 1971, p. 110.

[8] In comparison to the cited examples of slow and fast mutual interconversion of enantiomers at room temperature, (*R*)- and (*S*)-1,2,2-trimethylaziridines interconvert at an intermediate rate. Their diastereomeric association complexes were detected at 39°C (*K. Mislow*, Princeton, personal communication 1970).

[9] *E. Fahr, W. Rohlfing, R. Thiedemann, A. Mannschreck, G. Rissmann*, and *W. Seitz*, Tetrahedron Lett. *1970*, 3605.

[10] Prof. Dr. *E. Fahr*, Würzburg, kindly provided us with a sample of *(1)*. For preparation, see: *R. Thiedemann*, Dissertation, Universität Würzburg, 1968, p. 46.

[11] *A. Mannschreck* and *H. Münsch*, Tetrahedron Lett. *1968*, 3227.

[12] The mixture, m.p. 49—53°C, of 47% *(3)* and 53% *(4)* was obtained by the nitrosation of the corresponding secondary amine. Separation by thin layer chromatography yielded liquid *(4)* as well as *(3)*, m.p. 64—65°C [13].

[13] *A. Mannschreck* and *H. Münsch*, unpublished results; cf.: *H. Münsch*, Dissertation, Universität Heidelberg 1969.

[14] Cf.: *A. Mannschreck, H. Münsch*, and *A. Mattheus*, Angew. Chem. *78*, 751 (1966); Angew. Chem. internat. Edit. *5*, 728 (1966).

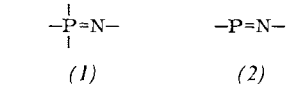
[15] We assume that the diastereomeric association complexes which are described here involve hydrogen bonds. Significant protonation of the enantiomers by *(2)* or *(5)* is unlikely since, apart from other reasons, the δ values which are measured in the presence of auxiliary compounds (Table 1) are very similar to those obtained in their absence.

[16] *A. Mannschreck, V. Jonas*, and *B. Kolb*, unpublished results.

[Bis(trimethylsilyl)amino][(trimethylsilyl)imino]phosphane, a Phosphazene with Tervalent Phosphorus[1]

By *Edgar Niecke* and *Wilhelm Flick*[*]

Compounds of four-coordinated phosphorus of type *(1)* are known in the form of phosphazenes, phosphane imides, and phosphorus nitrides or phosphoranylidenes[2]. However, the existence of a derivative of tervalent phosphorus with a phosphazene structural component *(2)* has not previously been proved[3].



(1) *(2)*

By preparing [bis(trimethylsilyl)amino][(trimethylsilyl)-imino]phosphane *(3)* from [bis(trimethylsilyl)amino]difluorophosphane[4] and lithium bis(trimethylsilyl)amide we have achieved the first synthesis of a phosphazene of coordination number 2.

(3) is a pale yellowish-green liquid, extremely sensitive to hydrolysis, which can be preserved for considerable times below 0 °C with protection from light; however, even traces of impurities cause rapid decomposition to very dark brown products.

The composition and structure of the compound were proved by elemental analysis, mass-, vibrational-, ^{1}H-, ^{29}Si-, and ^{31}P-NMR-spectra and by several characteristic reactions.

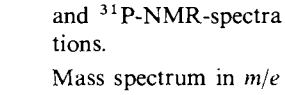
Mass spectrum in *m/e* (relative intensity): 278 (74%) *M*, 263 (100%) $M-CH_3$, 248 (1%) $M-2CH_3$, 218 (4%) $M-4CH_3$, 205 (8%) $M-Si(CH_3)_3$, 203 (22%) $M-5CH_3$, and further fragments.

Vibrational spectrum (IR, Raman, liquid) in the range $1500 > \tilde{\nu} > 400$ cm^{-1}: ≈1430 m, br, 1435 0.2 (dp); –, 1407 1.4 (dp); 1397 m, – all $\delta_{as}(CH_3)$; ≈1280 sh, 1282 (?); 1265 sh, 1264 (p); 1253 vs, 1253 (p); 1244 s, 1242 (?), all $\delta_s(CH_3)$ and ν(P=N) (rel. total intensity 9.5); 939 vs, 937 0.7 (dp) ν_{as}(SiN); 897 vs, 896 0.6 (p) ν(PN); 865 sh, 865 0.4 (dp); 846 vs, br, 850 0.1 (?); 835 sh, 836 0.7 (dp) all $\rho_{as}(CH_3)$; 768 m, 770 0.1 (dp); 753 m, 753 1.2 (dp) both $\rho_s(CH_3)$; 681 s and 675 s, ≈680 5.0 (dp); 645 m, 648, 8.0 (p); 621 m, 623 1.5 (p) all ν(SiC); 588 s, 590 9.5 (p); 449 s, 450 8.5 (p) ν(SiN) and ν_s(SiN). ^{1}H-NMR spectrum (20% solution in C_6H_{12}; TMS internal) at 25 °C: silylimino-H: δ = –0.10 ppm); $J_{H^{13}C}$ = 122.5, $J_{H^{29}Si}$ = 6.6 Hz); silylamino-H: δ = –0.31 ppm (d), J_{HP} = 1.52 Hz ($J_{H^{13}C}$ = 121, $J_{H^{29}Si}$ = 6.9 Hz). Coalescence of the silyl peaks at 77 °C[5]. With Δν = 12.6 Hz (60 MHz), $\Delta G_c^{\neq}$ amounts to 18.3 kcal/mol.

The ^{1}H- decoupled ^{29}Si-NMR spectrum (pure substance, TMS external) shows two doublets in the intensity ratio 2:1 with a highly shielded ^{29}Si nucleus in the silylimino group and a larger ^{29}Si—^{31}P interaction in the Si—N=P grouping: silylimino-^{29}Si: δ = 2.2 ppm, J_{SiP} = 26.8 Hz; silylamino-^{29}Si: δ = –8.2 ppm, J_{SiP} = 9.1 Hz.

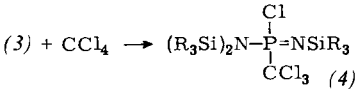
N-Silylated N=P—N compounds containing quadrivalent phosphorus also show a corresponding behavior in $\delta_{^{29}Si}$ and J_{SiP}[5a].

In the ^{31}P-NMR spectrum (50% solution in C_6H_{12}; H_3PO_4 external reference) the resonance signal (δ = –325 ppm) is found at extremely low field, in a region not reached by any phosphorus compound previously known[6]. Comparison with the chemical shifts of the three-coordinated aminophosphanes (δ = –78.4 to –133.6 ppm for compounds of the type $P(NR_2)_3$[6]) shows a frequency shift of *ca.* 200 ppm to lower field for the aminoiminophosphane—a result that is observed also on passing from alkyl- or aryl-phosphanes to the resonance-stabilized compounds of tervalent phosphorus with coordination number 2, namely the phosphabenzenes[7]. A lower shielding of the ^{31}P nucleus is also exhibited by the recently described dialkylaminophosphane cation,



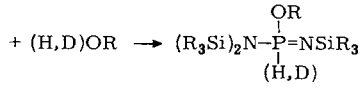
(δ^{31}_P = –274 ppm[8]), in which the phosphorus is likewise coordinated with two nitrogen atoms.

High reactivity of the considerably electrophilic phosphazene *(3)* is observable in a series of exothermic 1,1-additions[4] to phosphorus, such as:



(3) + CCl_4 → $(R_3Si)_2N-P(Cl)(CCl_3)=NSiR_3$ *(4)*

(4): Yield 95%; b.p. 118—119 °C/0.02 torr; ν(P=N) = 1365 cm^{-1}; ^{31}P-NMR (30% solution in C_6H_{12}; H_3PO_4 external standard): δ = –3.8 ppm.



(3) + (H,D)OR → $(R_3Si)_2N-P(OR)(H,D)=NSiR_3$

(5a, b)

(5): Yield 70—75%; b.p. 72—74 °C/0.2 torr; ν(P=N) = 1310 to 1315, ν(PH) = 2380, ν(PD) = 1715 cm^{-1};

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34 Göttingen, Hospitalstrasse 8—9 (Germany)

[1] Presented in part as a Lecture at the 4th European Fluorine Symposium in Ljubljana, Jugoslavia, August 1972.—This work was supported by the Deutsche Forschungsgemeinschaft.

[2] *H. R. Allcock*: Phosphorus-Nitrogen Compounds. Academic York New York 1972.

[3] *R. F. Hudson*: Structure and Mechanism in Organo-Phosphorus Chemistry. Academic Press, New York 1965.

[4] *E. Niecke* and *W. Flick*, to be published.

[5] An intermolecular migration of the 1,3-silyl group above room temperature has also recently been reported for $R_3SiN=P(OCH_3)_2N(SiR_3)_2$: *O. J. Scherer* and *R. Thalacker*, Z. Naturforsch. *27b*, 1429 (1972).

[5a] *E. Niecke*, to be published.

[6] *M. M. Crutchfield, C. H. Dungan, J. H. Letcher, V. Mark*, and *J. R. Van Wazer*, Top. Phosphorus Chem. *5*, 236 (1967).

[7] *G. Märkl* and *D. Matthes*, Angew. Chem. *84*, 1067 (1972); Angew. Chem. internat. Edit. *11*, 1017 (1972), and further literature cited therein.

[8] *S. Fleming, M. K. Lupton*, and *K. Jelot*, Inorg. Chem. *11*, 2534 (1972).

^{31}P-NMR (30% solution in C_6H_{12}, H_3PO_4 external standard): $\delta = -4.1$ *(5a)*, -3.8 *(5b)* ppm, $^1J_{PH} = 587.7$, $^1J_{PD} = 90.0$, $^3J_{HP} = 13.5$ *(5a,b)* Hz.

Experimental:

$PF_2N(SiR_3)_2$ (85 g, 0.37 mol) was added dropwise to a stirred suspension of $Li(NSiR_3)_2$ (100 g, 0.6 mol) in light petroleum (b. p. 40—60 °C) at room temperature in a 500-ml three-necked flask fitted with a reflux condenser and dropping funnel. After 3 hours' stirring, most of the solvent was removed and the residue was fractionally distilled under reduced pressure. The fraction passing over at 50 to 60 °C/0.01 torr was freed from residual $PF_2N(SiR_3)_2$ by being kept for 20 h at room temperature and 0.01 torr. Redistillation gave pure *(3)* at 62—63 °C/0.01 torr (yield 55 g, 53%).

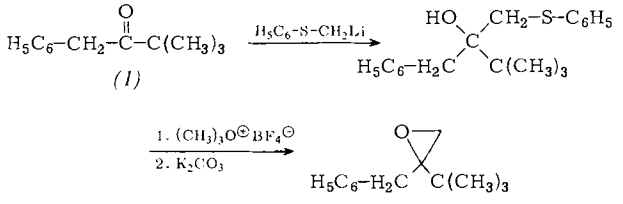
Received: December 6, 1972 [Z 793 IE]
revised: June 4, 1973
German version: Angew. Chem. 85, 586 (1973)

CONFERENCE REPORTS

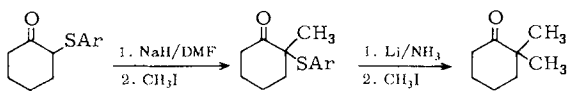
New Methods for the Alkylation of Carbonyl Compounds

By *R. M. Coates*[*]

Carbonyl compounds play a key role in organic synthesis, particularly in the formation of new carbon-carbon bonds. One such transformation, within the general class of nucleophilic alkylation reactions, is methylene (alkylidene) transfer, a conversion usually effected by sulfonium ylides. As in the case of the analogous methylenation reaction[1], we have found[2] that the structural limitations on methylene transfer by ylides (steric hindrance and proton abstraction) may be substantially reduced by use of a three reaction sequence originating with addition of phenylthiomethyllithium[3]. A pertinent example is the efficient methylene transfer to the sterically hindered and enolizable substrate, benzyl *tert*-butyl ketone *(1)*.



Electrophilic alkylation α to carbonyl functions constitutes an important method for creation of quaternary carbon centers in synthesis. We have recently developed some new procedures for regiospecific α-quaternization. By means of the sequential operations of alkylation-reduction-alkylation upon β-thioaryl ketones of type *(2)*, overall regiospecific geminal dialkylation of ketones may be achieved.



(2)

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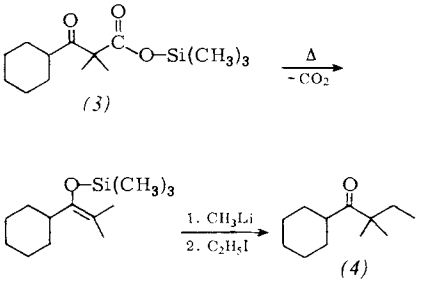
The regiospecific transformation of a quaternary-type β-keto ester to a quaternary alkyl ketone of type *(4)* may be carried out through pyrolytic decarboxylation of trimethylsilyl β-keto esters *(3)*[4] to trimethylsilyl enol ethers and subsequent enolate generation and alkylation.



These methods enhance the flexibility and scope of the relatively few known methods[5] for the regiospecific synthesis of α-quaternary ketones.

Lecture at Giessen, April 26, 1973 [VB 369 IE]
German version: Angew. Chem. 85, 630 (1973)

[1] *R. L. Sowerby* and *R. M. Coates*, J. Amer. Chem. Soc. *94*, 4578 (1972).

[2] A simultaneous and complementary investigation has been carried out by *C. R. Johnson* and *J. R. Shanklin*.

[3] *E. J. Corey* and *D. Seebach*, J. Org. Chem. *31*, 4097 (1966).

[4] *Y.-N. Kuo*, *J. A. Yahner*, and *C. Ainsworth*, J. Amer. Chem. Soc. *93*, 6321 (1971).

[5] *R. M. Coates* and *R. L. Sowerby*, J. Amer. Chem. Soc. *93*, 1027 (1971); *D. J. Pasto* and *P. W. Wojtkowski*, J. Org. Chem. *36*, 1790 (1971).

Studies on Methyleneimmonium Salts

By *Heinrich Volz*[*]

Methyleneimmonium salts are of interest from both a preparative and a mechanistic viewpoint. They have been discussed as reactive intermediates in the following reactions: Mannich reaction; Leuckart-Wallach reaction; Polonovski reaction; fragmentation of γ-halo amines.

The methyleneimmonium salts *(1)* used in our studies (perchlorates, tetrafluoroborates, and hexachloroanti-

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monates) were prepared by hydride abstraction with corresponding triphenylcarbenium salts from tertiary amines containing at least one methyl group[1]. The hydride abstraction occurred specifically at the methyl group (primary H > secondary H > tertiary H—kinetic product control).

$$H_3C{-}NR_2 + (C_6H_5)_3C^{\oplus}X^{\ominus} \rightarrow H_2C{=}\overset{\oplus}{N}R_2X^{\ominus} + (C_6H_5)_3CH$$

(1). IR: $\gamma_{C=N} = 1668$—1675; $\gamma_{CH_2} = 3140$—3155 cm^{-1}; NMR (δ, TMS): $CH_2 = 8.1$—8.3 ppm; J_{CH_2} (gem) = 7.2—7.6 Hz; $J_{^{13}C-H} = 186.2$ Hz.

Hydride abstraction from the methyl group of the tertiary amine can be regarded as a functionalization of this methyl group. Methyleneimmonium salts can be utilized preparatively for degradation and synthetic reactions: degradation takes place with water to give the secondary amine (demethylation), with acetate in acetic anhydride to give the acetylated secondary amine; reaction with Grignard reagents converts the methyl group into a larger ligand and Mannich bases are formed with C—H acidic compounds.

Investigations in connection with the Polonovski reaction confirmed the mechanism discussed by *Huisgen, Bayerlein,* and *Heydkamp*[2, 3].

Reduction of methyleneimmonium salts with formic acid (Leuckart-Wallach reaction) affords the tertiary amine in a yield exceeding 90%. Kinetic studies show that the reaction in formic acid (reagent and solvent) is of pseudo-first order. The kinetic isotope effect of this reaction is $k_H/k_D = 2.12$ for *N*-mesityl-*N*-methylmethyleneimmonium perchlorate *(1a)*. The activation parameters are $\Delta H^{\neq} = 21.8$ kcal/mol and $\Delta S^{\neq} = -23$ cal mol^{-1} deg^{-1}. The reaction is accelerated by addition of base. *N*-Mesityl-*N*-methylaminomethyl acetate reacts with formic acid some 5×10^4 times faster than *(1a)* under the same reaction conditions (substrate base catalysis).

Lecture at Mainz (Germany), April 19, 1973 [VB 368 1E]
German version: Angew. Chem. 85, 592 (1973)

[1] *H. Volz* and *H.-H. Kiltz*, Liebigs Ann. Chem. 752, 86 (1971).
[2] *R. Huisgen, F. Bayerlein,* and *W. Heydkamp*, Chem. Ber. 92, 3223 (1959).
[3] *H. Volz* and *L. Ruchti*, Liebigs Ann. Chem. 763, 184 (1972).

ABSTRACTS

Reviews

Abstracts of selected progress reports and review articles

Nuclear magnetic resonance and relaxation of molecules adsorbed on solids are the subject matter of a review by *H. Pfeifer* which considers the available literature up to 1971. A qualitative description of the principles of nuclear magnetic resonance and relaxation is followed by information regarding the results of nuclear magnetic relaxation theory and an account of the silica gel/benzene and NaX-zeolite/water systems and the interaction of OH groups on the surface of solids with adsorbed molecules. [Nuclear Magnetic Resonance and Relaxation of Molecules Adsorbed on Solids. NMR 7, 53—153 (1972); 393 references]

[Rd 564 1E—G]

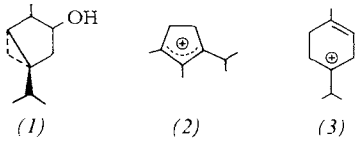
Evolution and biosynthesis of terpenoid pheromones and hormones are reviewed by *H. Z. Levinson*. The biosynthesis of terpenoid compounds was possible at a very early stage, according to inclusion material found in samples of Sudanese shale estimated as 2.5×10^9 years old. It is conceivable that isoprenoids assumed functions as pheromones and hormones after the transition from the abiogenic to the biochemical era. Terpenes and steroids act, *e.g.*, as pheromones in fungi, as hormones in higher plants, and as both in arthropods. The biosynthesis of terpenoid compounds that fulfil functions in communication, coordination, growth, and reproduction proceeds in a highly economic fashion. The same enzymatic steps frequently reoccur in numerous species at different levels of phylogenetic development. [Zur Evolution und Biosynthese der terpenoiden Phermone und Hormone. Naturwissenschaften 59, 477—484 (1972); 126 references]

[Rd 609 1E—M]

The mechanism of the oxo reaction is the subject of a report by *M. Orchin* and *W. Rupilius*. Although more that 2.5 million tons of alcohols are produced annually by the oxo process (also called hydroformylation), many details of the reaction mechanism are still unclear. The authors have therefore described the state of knowledge, and of speculation, as witnessed by the literature published up to 1971. [On the Mechanism of the Oxo Reaction. Catal. Rev. 6, 85—131 (1972); 79 references]

[Rd 566 1E—G]

A review of the chemistry of thujane derivatives from 1947 to 1972 is authored by *D. Whittaker* and *D. V. Banthorpe*. The absolute configurations and the conformations were determined by spectroscopy. Most of the thujane derivatives [four epimers of *(1)*] are obtained from the naturally



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

occurring thujanones by hydroboration and reduction. On oxidation the thujane ring is opened or modified, *e.g.* aromatized, or O functions are introduced. In concentrated

H_2SO_4 the four epimeric thujyl tosylates give solutions exhibiting the same NMR and UV spectra, which are assigned to the ion *(2)*. The biogenesis of thujanes could proceed *via* the ion *(3)*. [The Chemistry of Thujane Derivatives. Chem. Rev. *72*, 305—313 (1972); 115 references]

[Rd 615 IE—M]

Adsorption and catalysis on evaporated alloy films is the title of a comprehensive review by *R. L. Moss* and *L. Whalley*. The copper/nickel system has been most frequently studied, while a much lower number of publications is concerned with the palladium/gold, -/silver, and -/rhodium systems. The original authors' views are given for each reaction and alloy and described together with the reviewers' comments. [Adsorption and Catalysis on Evaporated Alloy Films. Advan. Catal. *22*, 115—189 (1972); 165 references]

[Rd 576 IE—G]

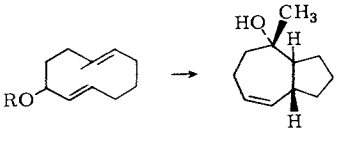
Synthetic applications of cyclopropene cycloadditions are discussed by *M. L. Deem*. Such cycloadditions permit the incorporation of allyl, cyclopropyl, oxopropenyl, and oxocyclopropanyl groups, or their elimination or hydrogenation fragments, into five- and six-membered carbo- and heterocyclic systems. Suitable reagents include cyclopropene, cyclopropenone, cyclopropenethione, and substituted cyclopropeneimides, as well as substituted calicenes and other triafulvenes. [Cyclopropenes as Reagents for Synthesis. Cycloaddition Reaction with Cyclopropenes. Synthesis *1972*, 675—619; 128 references]

[Rd 606 IE—M]

The relationships between the chemical structure of phospholipids and biomembranes is the topic of an article by *L. L. M. van Deenen*. The combination of lipophilic and hydrophilic regions in the one molecule renders phospholipids ideal building blocks for biological interfaces and, in keeping with present-day concepts, crucial for the formation of all biomembranes. The study of phospholipids in artificial membrane systems shows that simple diffusion of nonelectrolytes and the effectiveness of carrier-induced transport processes depend on the lipid parameters. These observations have been confirmed with natural membranes. [Phospholipide. Beziehungen zwischen ihrer chemischen Struktur und Biomembranen. Naturwissenschaften *59*, 485—491 (1972); 39 references]

[Rd 608 IE—M]

Progress in the synthesis of hydroazulenes (completely or partially hydrogenated azulenes) that are of interest, *inter alia*, as perfumes and potential pharmaceuticals, is reported by *J. A. Marshall*. Stereoselective syntheses are possible 1) by rearrangement of bicyclic compounds having cyclohexane rings, 2) by cleavage of tricyclic compounds, and



(1), R = p-O_2N-C_6H_4-CO

3) by cyclization of olefins such as *(1)*. [Progress in Hydroazulene Synthesis. Synthesis *1972*, 517—525; 38 references]

[Rd 611 IE—M]

The theory of electronic transitions between states of different total spin is outlined by *L. L. Lohr jr.* There are essentially two mechanisms by which these forbidden transitions can gain intensity: in isolated species (in gases, dilute solutions, and with low concentrations of the transition metal ion in a nonabsorbing solid) by spin-orbit coupling; in bi- or polynuclear complexes or with higher concentrations of absorbing ions in solids by exchange interaction between neighboring ions. This interaction manifests itself by a breakdown of Beer's law and sometimes by the occurrence of electronic overtone and combination bands caused by simultaneous electronic transitions in two like or different ions. [Spin-Forbidden Electronic Excitations in Transition Metal Complexes. Coord. Chem. Rev. *8*, 241—259 (1972); 74 references]

[Rd 630 IE—H]

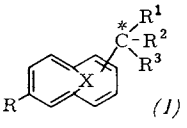
A survey of the coordination chemistry of trivalent iron is given by *S. A. Cotton*. It begins with an account of the physical methods relevant for the elucidation of iron(III) complex structures. The complexes that can be isolated in the solid state are then described in the order of the donor atoms. A table with the known X-ray structures of iron(III) complexes (about 30) completes the review. [Some Aspects of the Coordination Chemistry of Iron(III). Coord. Chem. Rev. *8*, 185—223 (1972); 263 references]

[Rd 631 IE—H]

Patents

Abstracts of selected "Deutsche Offenlegungsschriften" (DOS), *i. e.* provisionally published specifications as filed with the German Patent Office

2- or 3-Substituted 1,6-bridged cyclodecapentaenes *(1)* are chemotherapeutically active compounds. Depending on the nature of the substituents, the compounds *(1)* exhibit



(1)

R = H, alkyl, cycloalkyl, alkoxy, carbocyclic acyloxy; R^1, R^2 = H, alkyl; $R^1 + R^2 = >CH_2$; $R^1 + R^2 + C^* =$ cycloalkyl; R^3 = CHO, CH_2OH, or hydrolyzable esters or ethers as precursors thereof, COOH, COOalkyl, COOalkali metal, $CONH_2$, $CON(alkyl)_2$; X = CH_2, CCl_2, CF_2

anti-inflammatory, analgesic, and antipyretic activity, or serum cholesterol-depressing and fibrinolytic activity. The cyclodecapentaenes *(1)* can be prepared by several methods, which are discussed in detail. The organic groups mentioned all contain only a few C atoms. [DOS 2051012; Syntex Corp., Panama]

[PR 89 IE—N]

Degradable manufactured articles, particularly films, whose decomposition rate depends on exposure to sunshine and on the temperature, consist of polymers having at least 50 wt.% of 1-butene units and contain 0.001 to 30 wt.% of stabilizers, the quantity of the latter being such that the

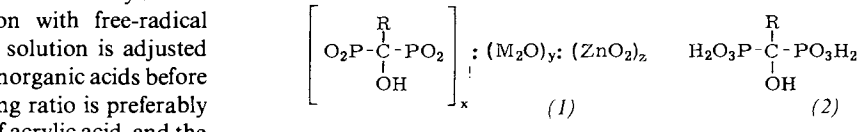
stability is 5000 to 70000 temperature-corrected Langley units. The polymer may in particular be poly-(1-butene) having a molecular weight of 10000 to 3000000, preferably 40000 to 1500000, which should have an isotacticity of more than 70%. Conventional stabilizers are used. The stability of the products is adjusted to suit the prevailing climatic conditions and the particular application intended. For example, it is possible to produce agricultural covering films that decompose at the conclusion of the growth period of the plants in question, with the result that their mechanical removal before the ground is used again is no longer necessary. [DOS 2158379; Princeton Chemical Research Inc., Princeton, N.J.]

[PR 68 IE—S]

Thermally reversible coacervates, *i.e.* polymer solutions that reversibly undergo phase separation with formation of polymer-rich aqueous phases at certain temperatures, are obtained when mixtures of acrylamide and acrylic acid are polymerized in aqueous solution with free-radical catalysts and the pH of the polymer solution is adjusted to values below 3.3 by the addition of inorganic acids before or after the polymerization. The mixing ratio is preferably 50 mol-% of acrylamide to 50 mol-% of acrylic acid, and the total concentration should be between 5 and 15 wt.%. Examples of inorganic acids mentioned are sulfuric acid and hydrochloric acid. The more acidic the solution, the higher is the temperature at which the coacervate is formed, *e.g.* 30 °C at pH 3.0 and 40 °C at pH 1.5. There is also a dependence on the molecular weight of the polymer. The synthetic coacervates can be used in the same way as gelatin-gum arabic coacervates *e.g.* for the production of coatings, microcapsules, *etc.* If cooled objects are immersed in a coacervate solution above the transition temperature, the coacervate is deposited on these objects in the form of a coating. [DOS 2060571; Farbenfabriken Bayer AG, Leverkusen]

[PR 66 IE—S]

New vitreous compositions having the general formula *(1)* are excellent corrosion inhibitors in aqueous systems, particularly for iron and steel, and can also be used to combat boiler scale and as dispersing agents. The water-soluble materials *(1)* contain about 5 to 21 wt.% of zinc, and unlike the phosphates used in the past, they do not form undesirable deposits. The alkali metal- and/or ammonium-zinc "mixed glasses" have been prepared by evaporation of aqueous solutions obtained from zinc salts,



(1) *(2)*

R = alkyl ($C_1 - C_5$), phenyl, benzyl; M = alkali metal and/or NH_4; $x = 1$; $y = 1$ to 1.75; $z = 0.25$ to 1

α-hydroxy-1,1-diphosphonic acids *(2)*, and alkali metal and/or ammonium hydroxide with adjustment of the pH to specific values. [DOS 2151552; Calgon Corp., Pittsburgh, Pa.]

[PR 77 IE—U]

BOOK REVIEWS

Organic Reactions and Orbital Symmetry. By *T. L. Gilchrist* and *R. C. Storr*. Cambridge University Press, London 1972. 1st ed., viii, 271 pp., numerous figures bound £ 1.80.

This is an outstanding description of one-step reactions (also known as concerted, synchronous, or pericyclic reactions), which can be wholeheartedly recommended to the chemistry student. The theory and classification of such reactions developed by *Woodward* and *Hoffmann* was a revolutionary innovation in organic chemistry. The significance of this theory and the equivalence of all qualitative theoretical derivation concepts (orbital symmetry, HOMO/LUMO and aromatic transition state) are presented objectively and with many practical examples in typical Anglo-Saxon manner: clearly, concisely, and presupposing neither theoretical knowledge nor familiarity with the numerous reactions discussed. It is repeatedly stressed that while the Woodward-Hoffmann "rule" gives the steric course for "allowed" synchronous reactions, a reacting system naturally chooses the path having the lowest energy, which is often a multi-step process.

The fact that the terms "stereospecific" and "stereoselective" (*e.g.* pp. 13 and 154) are not used in accordance with the generally accepted definition (textbooks by *Eliel* and *Mislow*) and the selection of an awkward representation for the systems with odd numbers of p orbitals (allyl and pentadienyl, pp. 26, 113, and 208) are only minor faults.

After the classification of the reaction mechanisms and an introduction to the general theory of one-step reactions, the book contains chapters on electrocyclic transformations, cycloadditions and their reversal (thermal, photochemical, and metal-catalyzed) including pericyclic reactions, sigmatropic shifts, and substitution, addition, and elimination mechanisms. The authors cite relevant articles and reviews, extending up to 1971, for further reading in special fields.

Dieter Seebach [NB 135 IE]

Charge Transfer Interactions of Biomolecules. By *M. A. Slifkin*. Academic Press, London—New York 1971. 1st ed., xx, 271 pp., numerous figures and tables bound $ 16.50.

Even the scientific book market from time to time comes up with a curiosity, a case in point being the present volume, which opens after the model of Genesis 1 with

the lapidary sentence: "All molecules are built up from atoms". (Oh, quite so!). It is not surprising, therefore, that the hydrogen bond is referred to in the Foreword as a special case of "charge transfer complexing", and that by the time he reaches the end the reader must be convinced that Man, God, the world, the cancer problem, and Sigmund Freud are nothing but charge transfer complexes.

Since *Szent-György*'s "Introduction to Submolecular Biology", charge transfer complexes have indeed developed into a problem of bio-traumatology. Father *Mulliken* was wide of the mark with his sober but (like much that is sober) dull definition, and the spectrum of phenomena covered by it extends to "charge transfer complex without charge transfer". The author appeals to predecessors in the field (*R. Foster:* "Organic Charge Transfer Complexes", London 1969), who evidently regard all weak chemical interactions as charge transfers, since this has become accepted in the literature (p. 10).

Once his wide field has been marked off in this way, the author ploughs on heroically. On p. 47 we learn that water is "the obvious solvent" for biochemicals, since it is both very transparent and very cheap. On p. 55 the last veil drops: there are now also charge transfer complexes that are formed only very slowly, *e.g.* from α-amino acids and chloranil. The author makes generous references to his own research data here, and has apparently taken no great pains to rule out the possibility of a slow chloranil-catalyzed autoxidation.

The charge-transfer idea then becomes a total farce *e.g.* in connection with complexes of the same amino acids and riboflavin. The author is fair enough to admit that doubt was cast on his interpretation as early as 1965 by *Kosower*, who very reasonably interprets the association of amino acids and flavin "as due to hydrophobic bonding of the amino acids to the flavin, the spectral changes being simply perturbation effects."

Whether true charge transfer effects as defined by *Mulliken* are biologically relevant remains to be established, probable as it may be in certain cases of biological signal transmission. Further knowledge on this point will be obtainable only through extremely sharp physicochemical differentiation. The present book merely thickens the mist over this landscape.

Peter Hemmerich [NB 153 IE]

Recent Books

The following books have been received by the editor. Detailed reviews will not be published in all cases because of the limited space available under this heading in the journal.

Ion Association in Proton Transfer Reactions. By *J. R. Jones.* **Use of ESR for the Quantitative Determination of Gas Phase Atom and Radical Concentrations.** By *A. A. Westenberg.* Vol. 7/1 of the Series "Progress in Reaction Kinetics", edited by *K. R. Jennings* and *R. B. Cundall.* Pergamon Press, Oxford, New York, Toronto, Paris, Braunschweig 1973. 1) pp. 1—21; 2) pp. 22—82, stitched £ 1.75.

Molecular Structure and Properties. Edited by *G. Allen.* Vol. 2 of the series "Physical Chemistry Series One". Edited by *A. D. Buckingham.* Butterworths, London—University Park Press, Baltimore 1972. 264 pp., bound £ 10.00.—A volume in the series "MTP International Review of Science".

Electrochemistry. Edited by *J. O'M. Bockris.* Vol. 6 of the series "Physical Chemistry Series One". Edited by *A. D. Buckingham.* Butterworths, London—University Park Press, Baltimore 1973. 332 pp., bound £ 10.00.—A volume in the series "MTP International Review of Science".

Thermochemistry and Thermodynamics. Edited by *H. A. Skinner.* Vol. 10 of the series "Physical Chemistry Series One". Edited by *A. D. Buckingham.* Butterworths, London—University Park Press, Baltimore 1972. 259 pp., bound £ 10.00.—A volume in the series "MTP International Review of Science".

Techniques of High Resolution Nuclear Magnetic Resonance Spectroscopy. By *W. McFarlane* and *R. F. M. White.* Butterworths, London 1973. 137 pp., bound £ 3.50.

Contents: Introduction; basic theory of NMR spectra; interpretation of hydrogen NMR spectra; the NMR spectrometer; experimental techniques; double resonance techniques; NMR spectra of carbon-13 and other nuclei.

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Structure and Function of Nucleosides and Nucleotides[1]

By Wolfram Saenger[*]

The nucleosides participating in biological processes consist of a sugar and a heterocyclic nucleobase; the nucleotides, which occur as monomers and as building units of polymeric nucleic acids, contain an additional phosphoester group. The complexity of the molecules leads to a complex stereochemistry with which the present progress report is concerned. Particular attention will be devoted to conformational considerations at the sugar groups, the *syn-anti* conformation, the position of the C(5′)—O(5′) bond relative to the sugar group, and the conformation of the phosphoester bonds. The article touches upon base pairing and base stacking, as well as forces stabilizing the *syn* conformation, and also deals with the reaction mechanism of the enzyme pancreatic ribonuclease as established from the stereochemistry of nucleotides and the mechanisms of action of the antileukemia drug 6-azauridine and the antibiotic actinomycin D. Views on the effects of the unusual structures of the "rare" nucleosides 4-thiouridine, isopentenyladenosine, and dihydrouridine on the structure of transfer ribonucleic acid are also presented.

1. Introduction

Biological processes are determined at a molecular level by amino acids and nucleosides. The nucleosides are made up of a sugar group to which a heterocyclic nucleobase is bound by a β-*N*-glycosidic linkage (Fig. 1). The sugar group in the ribonucleosides is a D-ribose, and that in the deoxyribonucleosides is a D-*erythro*-D-pentose (2′-deoxy-D-ribose). The nucleobases, the actual active groups of the nucleosides, are amino- and hydroxyl-substituted purine and pyrimidine derivatives: adenine (A); guanine (G); cytosine (C); uracil (U); thymine (T). The corresponding ribonucleosides are designated adenosine (rA), guanosine (rG), cytidine (rC), uridine (rU), and deoxyribonucleosides by the prefix deoxy- and the abbreviations dA, dG, dC, dT[2]. The nucleotides (adenylic, guanylic, cytidylic, uridylic, thymidylic acids) contain an additional phosphoester group at the 3′- or 5′-hydroxyl function of the sugar group. Moreover, cyclic intramolecular 3′,5′- or 2′,3′-phosphodiesters also exist (Fig. 1).

In the biopolymers deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) the nucleotides are linked *via* internucleotide 3′,5′-phosphodiester bonds; their sequence contains the biological information. Depending on their particular biological function, both kinds of nucleic acids can exist as a single strand (coil) or as double-stranded complexes with a right-handed helical structure. In these complexes two nucleic acid chains are invariably arranged in an antiparallel fashion such that strictly complementary bonding occurs between opposite nucleobases A and U(T), and G and C, *via* specific hydrogen bonds[3]. This base pairing assists in stabilizing the structure of the double-stranded nucleic acids and is essential for biological information transfer from nucleic acid to nucleic acid and from

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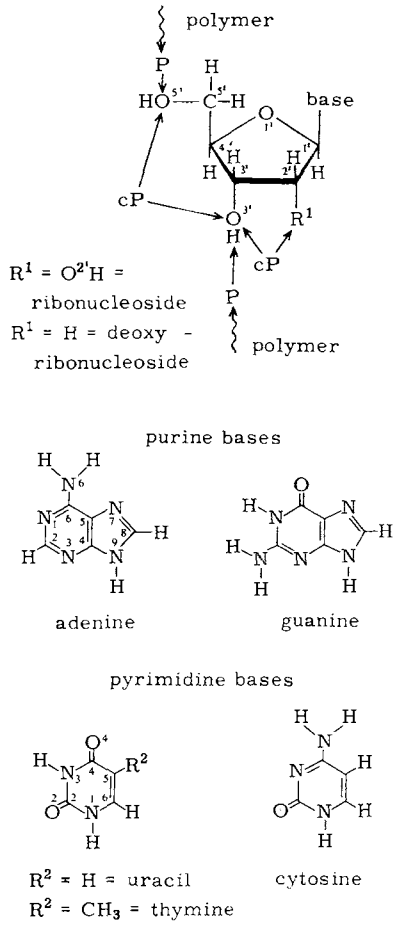


Fig. 1. Chemical structure and nomenclature of nucleosides and nucleotides. "cP" and "polymer" refer to the hydroxyl groups of the sugar group involved in the formation of cyclic phosphodiesters and 3',5'-internucleotide bonds (in the polymeric nucleic acids). Relevant examples may be found in Figs. 11–13. Uridine is present in ribonucleosides, and thymidine in deoxyribonucleosides.

nucleic acid to protein (protein biosynthesis) in which an information-carrying nucleic acid is read off as a template[4–6].

However, nucleotides participate in biological processes not only as components of nucleic acids but also as monomers in the form of "high-energy" nucleoside 5'-triphosphates as energy donors, as substrates of various enzymes, and as components of numerous coenzymes[4–6]. Naturally occurring modified nucleosides and nucleoside phosphates also play an important role as antibiotics[7], and synthetic nucleosides and their 3'- or 5'-phosphoesters are employed as drugs and for the study of molecular biological reactions. This clearly illustrates the intimate connection between the molecular structure and the biological function of a nucleotide.

The structure of a nucleotide or nucleoside is described by:

1. the conformation of the sugar group and the phosphoester bond;

2. the conformation at the glycosidic linkage, *i.e.* the position of the base relative to the sugar group;

3. atomic bonding distances and angles within a molecule;

4. intermolecular interactions, especially hydrogen bonding (base pairing) and base stacking.

These parameters can be determined by various methods providing data of greater or lesser general validity. Results of X-ray structural analyses constitute the main substance of this paper since they provide the most comprehensive and unequivocal information.

2. General Features of X-Ray Structural Analysis and the Structural Parameters of Molecules; Dihedral Angles

In structural analysis by X-ray diffraction a crystal of the substance under study is irradiated with monochromatic X-rays and the radiation diffracted by the crystal lattice is registered on photographic film, or even better by scintillation counters[8,9]. The symmetry of the reflection pattern and the distances between the reflections afford the crystallographic space groups ("symmetries") and the dimensions of the unit cell, while the intensities and relevant phase angles yield the positional coordinates of the individual atoms in the asymmetric system of the unit cell. Owing to the favorable experimental data/parameter ratio of between six and ten for each three coordinates and six atomic vibrational parameters of the atoms the coordinates of all the atoms except the protons can be determined to within an accuracy of about 0.003 Å[*]. Thus atomic bonding distances and angles, which generally lie in the range of 1.2 to 2.0 Å and 90 to 130°, respectively, can be given with standard deviations of *ca.* 0.005 Å and 0.4°[10].

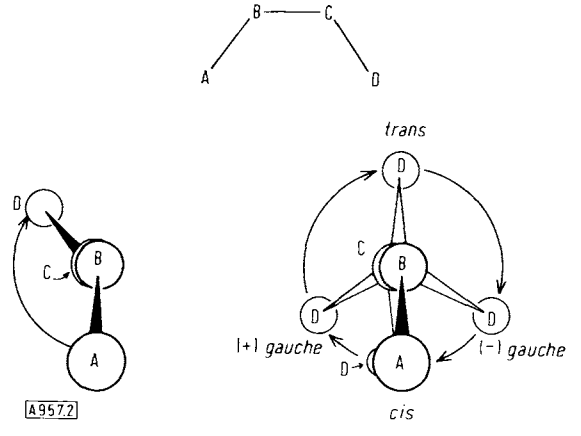


Fig. 2. Definition of the dihedral angles and the *cis*, *trans*, *gauche* regions.

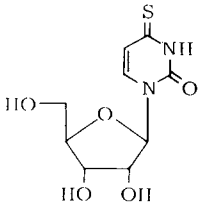
Dihedral (torsional) angles are employed in describing the conformation of a molecule[11]. In the atomic group A—B—C—D (Fig. 2) these angles denote the angle between the bonds A—B and C—D looking along the B—C bond (*i.e* with C behind B). The dihedral angle A—B—C—D is zero when A—B and C—D are *cis*-planar to each other, and is regarded as positive when C—D is twisted clockwise relative to A—B.

A dihedral angle is designated *cis* or *trans* when the angle is approximately 0 or 180° and as (+) *gauche* or (−) *gauche* when the angle is about +60 or −60°.

[*] For technical reasons the positions of the protons of an organic molecule can only be given with a tenfold lower accuracy than those of the other atoms.

On crystallization of a substance, intermolecular forces such as van der Waals forces, dipole forces, ionic and hydrogen bonding forces become operative[4, 12] which are almost completely absent in solution or in the gaseous state at suitable dilutions. X-Ray structure analyses revealed that these intermolecular forces affect the bonding distances hardly at all, and the bonding angles but slightly; however, they have a considerable effect on the dihedral angles. It thus follows that molecules often crystallize in a form other than that of minimum energy and that conformational studies by X-ray structural analysis only give unequivocal results when a series of similar compounds is analyzed.

This is precisely the case for nucleosides and nucleoside phosphates; perusal of the available data provides an insight into energy minima, rotational barriers, and rare conformations, and into the formation of hydrogen bonds and the packing of the molecules in the crystal lattice. Figure 3 illustrates the crystal structure of 4-thiouridine as the result of a typical X-ray structure analysis[13]. The



4-thiouridine

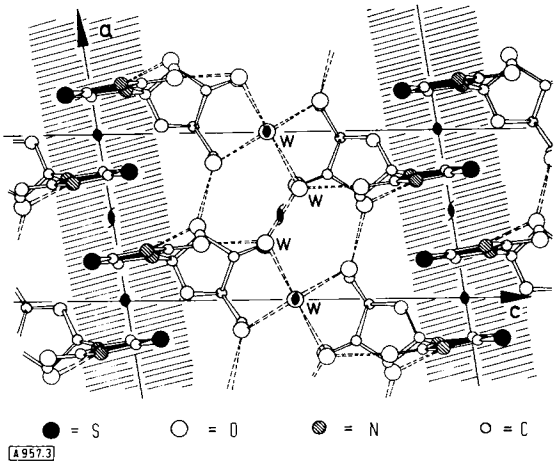


Fig. 3. Crystal structure of 4-thiouridine (projection along the *b* axis, space group monoclinic, C 2). Hydrogen bonds are shown as dashed lines and regions of hydrophobic character are emphasized by hatching. The 4-thiouracil rings are almost perpendicular to the plane of the paper and the molecules of water of hydration are labeled W.

structure is viewed along the crystallographic *b* axis. The planes of the 4-thiouracil groups are almost perpendicular to the plane of the paper and are arranged parallel to one another in a ribbon of hydrophobic character. An arrangement parallel to the plane of the paper is assumed by the ribose groups, together with included water of hydration; these groups form a band of predominantly hydrophilic nature which is stabilized and characterized by numerous hydrogen bonds.

3. Structure of Nucleosides and Nucleotides

3.1. Geometry of the Bases

Figure 4 shows the bond lengths and bond angles in the most important planar nucleobases[14]. The preponderance of double and single bond character respectively is apparent from the interatomic distances in the carbonyl and amino groups[12]; no tautomeric forms other than those shown in Figure 4 have been found in the crystal structure of the nucleosides although other forms have been predicted theoretically[15] and detected experimentally[16].

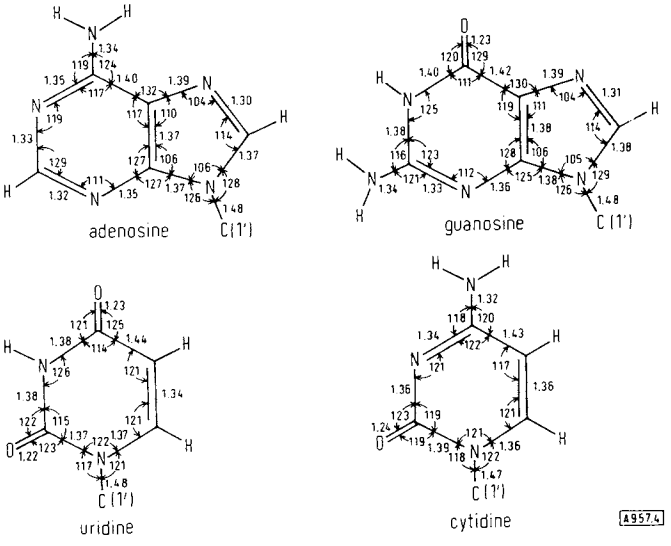


Fig. 4. Atomic bonding distances [Å] and angles [ ] in nucleosides (rounded off values from ref. [14]). Standard deviations 0.01 Å and 1°. Only C(1') of the ribosyl group is shown.

X-Ray structure analyses indicate that adenosine is protonated at N(1), guanosine at N(7), cytidine at N(3), and uridine at O(4)[14]. Protonation slightly modifies the geometry of the bases: the bond lengths change in accord with the new resonance structures and the bond angles at the protonated nitrogens are widened by about 5°[17–19].

3.2. Geometry of the Sugar Group

Figure 5 shows the average geometric data established for the sugar group. The atomic bonding distances and angles differ slightly but significantly depending on the nature and conformation of the sugar rings; however, we shall not go into these differences here.

Generally speaking, the C(4')—O(1') bond is longer than the O(1')—C(1') bond, an observation explainable in terms of the differing substitution at C(4') and C(1'). All the other bond lengths and angles lie in the "normal" range[10], although individual differences do occur.

Like the atoms of other five-membered rings, the five atoms of the ribose or deoxyribose rings are arranged in an envelope or half-chair conformation. Substituent effects lead to preference of those conformations in which the

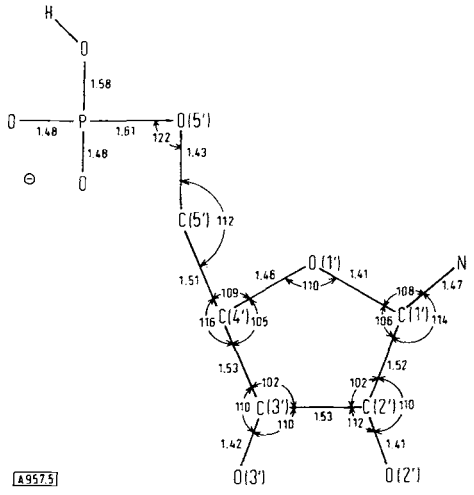
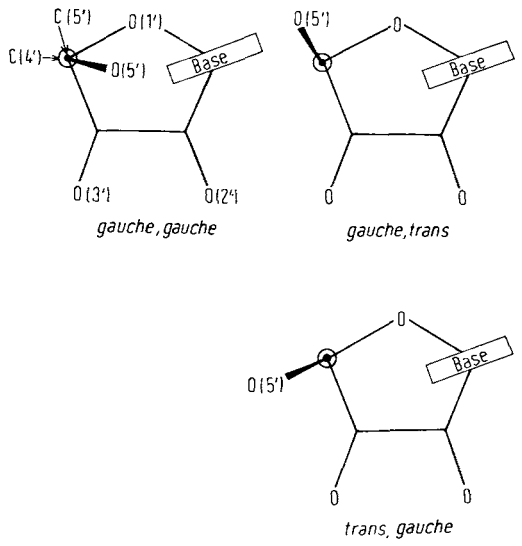


Fig. 5. Atomic bonding distances [Å] and angles [°] in nucleotides (averages values). Only the nitrogen atom on C(1') of the bases is shown.



atoms C(2') and C(3') are displaced by about 0.5 Å from the plane through the other atoms C(4')—O(1')—C(1'). Atoms lying on the same side of this plane as C(5') are designated *endo* and those on the other side *exo*[20]. The envelope and half-chair conformations observed in riboses and deoxyriboses are illustrated in Figure 6.

The envelope conformations C(2')-*endo* and C(3')-*endo* are encountered equally commonly; C(3')-*exo* has only been observed in three deoxyribonucleosides, and C(2')-*exo* not at all[21,22]. The transition between corresponding half-chair and envelope conformations occurs readily in the horizontal direction of Figure 6 but is subject to energy barriers in the vertical direction. The most unambiguous conformational description is provided by the endocyclic dihedral angles which lie in the range given in Figure 8.

The C(5')—O(5') bond can rotate relative to the sugar ring, assuming three possible conformations, designated *gauche, gauche*, *gauche, trans*, or *trans, gauche* depending upon whether the angles φ_{OO}, O(5')—C(5')—C(4')—O(1'), and φ_{OC}, O(5')—C(5')—C(4')—C(3'), lie close to $-60°$, $+60°$, to $+60°$, 180°, or to 180°, $-60°$[23] (Fig. 7).

Energy calculations predict approximately equal contributions from the three conformations[24]. However, crystallographic and spectroscopic data indicate an overwhelming preference for the *gauche, gauche* conformation

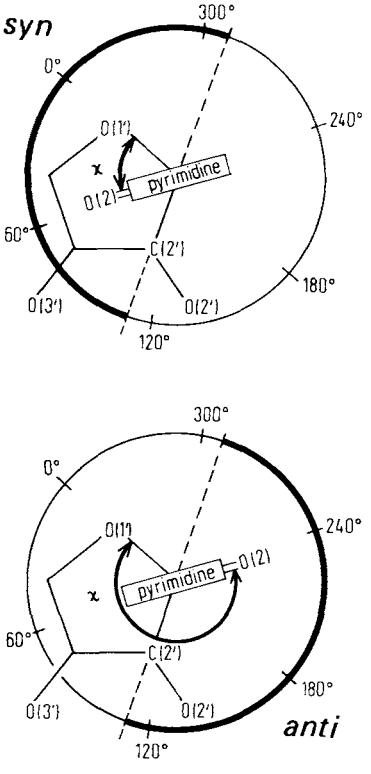


Fig. 7. Conformations at the C(4')—C(5') and C(1')—N bonds. See text for definition of the angle χ.

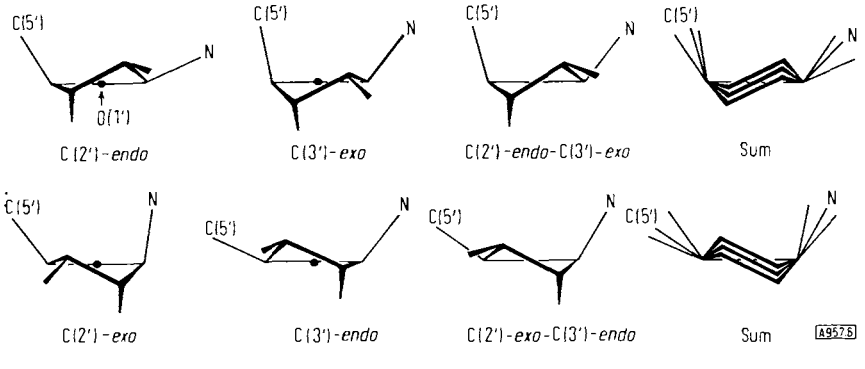


Fig. 6. Representation of the various sugar conformations. Depending on the conformation of the sugar the relative positions of the atoms C(5') and N(1) of the nucleobase can vary by up to about 0.5 Å.

over the other two[25]; an interpretation could lie in the exclusive ability of this conformation to engage in intramolecular C(6)—H ··· O(5') and C(8)—H ··· O(5') hydrogen bonding between the O(5') atom and the pyrimidine and purine base respectively[26].

3.3. Conformation about the Glycosidic C(1')—N Bond

Rotation of the base around the glycosidic bond relative to the sugar group is not free but subject to steric hindrance, primarily by the *endo* proton at C(2')[25]. Thus the nucleosides and nucleoside phosphates can exist in two conformations, designated *syn* and *anti*, depending upon whether O(2) in pyrimidine nucleosides or N(3) in purine nucleosides lies above the plane of the sugar group or points away from it[27,13] (Fig. 7). The position of the base is given by the dihedral angle χ_{CN}, *i.e.* O(1')—C(1')—N(1)—C(2) in pyrimidine nucleosides and O(1')—C(1')—N(9)—C(4) in purine nucleosides[28]. The *syn* and *anti* conformations are defined by values of χ_{CN} between about 290 to 110° and 110 to 290° respectively.

3.4. Conformation of the Phosphoester Bonds

The conformation observed in monomeric phosphodiesters and mononucleotides and in double-stranded helical nucleic acids are summarized in Figure 8.

Apart from adopting the conformations of the helical nucleic acid structures in which the dihedral angles are determined by geometrical conditions (formation of the right-handed helix), monomeric nucleotides can also assume a whole variety of conformations[21,22]. The angles ϕ(O(5')—C(5')), $180\pm40°$, and ψ(C(5')—C(4')), $60\pm25°$, are exceptional in that they are limited to the values given in both nucleotides and polymeric nucleic acids, probably due to the (base) C—H ··· O(5') hydrogen bonding mentioned above which stabilizes these conformations[29]. Moreover, the angle ψ'(C(4')—C(3')) assumes two values, $80\pm10°$ and $150\pm20°$, arising from the C(3')-*endo* and C(2')-*endo* or C(3')-*exo* sugar conformations.

Generalizing, it may be said that the various conformations of the sugar phosphate skeleton in double-stranded nucleic acids of helical structure are due primarily to the mobility of the sugar group. In monomeric nucleotides and in single-stranded nucleic acids, however, the high degree of flexibility arises from the numerous possible conformational angles of the sugar moiety and the phosphoester bond.

4. Correlation between Structure and Function of Nucleosides and Nucleotides

The above structural parameters of nucleosides and their phosphates will now be interpreted with the aid of examples. Since we cannot possibly consider all the studies published hitherto[30], just a few results of a characteristic nature will be given which permit a correlation between structure and function.

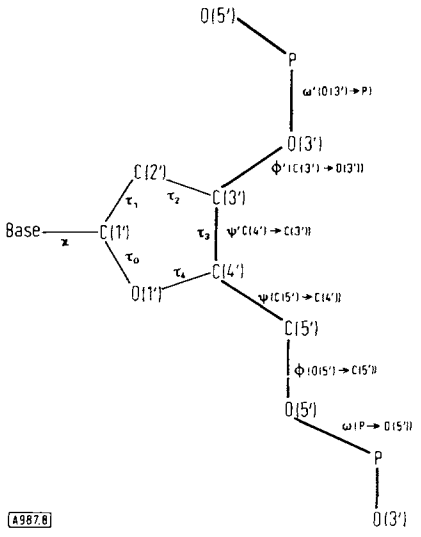


Fig. 8. Dihedral angles in nucleotides. The endocyclic angles describe the sugar conformation, and the angles ψ, ϕ, ω, ψ', ϕ', ω' the conformation of the sugar phosphate chain; *e.g.* ψ(C(5')—C(4')) denotes the angle O(5')—C(5')—C(4')—C(3'). M and M + P indicate whether the values of the angles apply only to the monomers (M) or also to polymeric helical nucleic acids (M + P).

angles in sugar group:

C(2')-*endo* and C(3')-*exo*	$\tau_1, \tau_3 = 30\pm10°$ $\tau_0, \tau_2 = 330\pm10°$ $\tau_4 = 0\pm10°$	
C(3')-*endo*	$\tau_1, \tau_3 = 330\pm10°$ $\tau_2, \tau_4 = 30\pm10°$ $\tau_0 = 0\pm10°$	

angles in sugar phosphate chain:

ω'(O(3')—P)	$290\pm20°$ $170\pm10°$ $70\pm10°$	P + M M
ϕ'(C(3')—O(3'))	$210\pm40°$ $250\pm20°$	P + M M
ψ'(C(4')—C(3'))	$80\pm10°$ $150\pm20°$	C(3')-*endo* C(2')-*endo*- C(3')-*exo* } P + M
ψ(C(5')—C(4'))	$60\pm25°$ $180\pm10°$ $290\pm10°$	P + M M
ϕ(O(5')—C(5'))	$180\pm40°$	P + M
ω(P—O(5'))	$290\pm20°$ $70\pm10°$	P + M M

4.1. Base Pairing

The regular structure of double stranded helical DNA and RNA is a consequence of coplanar coupling between the nucleobases A and U(T) and of G and C *via* specific N—H ··· O and N—H ··· N hydrogen bonds of the Watson-Crick type[3] (Figs. 9a and 9b). Stacked one above another these base pairs form the (hydrophobic) nucleus of the helix around which the (hydrophilic) sugar phosphate chain is wound in a right-handed fashion. The most striking feature of the Watson-Crick base pairs is that they are mutually isomorphous and that the glycosidic linkages,

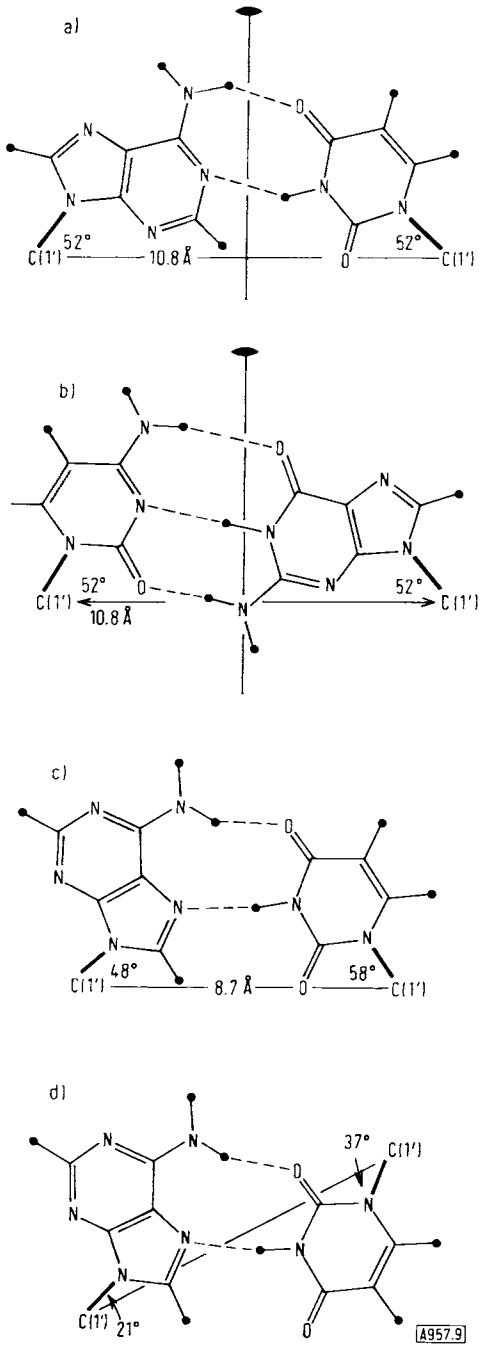


Fig. 9. Structure of the isomorphous a) A:U(T) and b) G:C base pairs according to *Watson* and *Crick*, and c) of the A:U(T) base pair according to *Hoogsteen* and d) the "inverse" Hoogsteen pair. The twofold axes relating the glycosidic bonds are shown in 9a and 9b. The N—H ··· N or N—H ··· O hydrogen bonds are about 2.9 Å long.

and thus the attached sugar phosphate chain, can be superimposed on rotation around twofold axes.

No less than 24 other pairing schemes between monomeric nucleosides are also conceivable in addition to the base pairs of the kinds illustrated in Figure 9[39], but only few have so far been found experimentally. Spectroscopic measurements[40,41] on nucleoside analogs in aprotic solvents indicated that not only heterologous base pairs (between different bases) but also homologous base pairs (between identical bases) can be formed. However, the heterologous A:U(T) and G:C complexes are more stable than all other conceivable hetero- or homologous base combinations by a factor of at least ten.

Co-crystallization of equimolar amounts of guanosine and cytidine derivatives always gives complexes with Watson-Crick base pairing, whereas complexes of adenosine and uridine (thymidine) derivatives have so far only been found to exhibit Hoogsteen base pairing (Figs. 9c and 9d)[42,14]. This finding would suggest that the Watson-Crick type A:U(T) base pairs, unlike the G:C base pairs, are not preferred energetically in helical RNA and DNA but result from steric contraints of the sugar phosphate chain.

4.2. Base Stacking

The nucleobases are of predominately aromatic hydrophobic character and tend to adopt a stacking arrangement in a hydrophilic environment and on crystallization. Parallel aromatic planes are separated by the expected van der Waals distance of 3.4 Å.

Base stacking is stabilized mainly by interaction between the dipoles of the amino or carbonyl groups and the neighboring π-electron systems[43] and by van der Waals forces[44].

The stacking properties of thio- and halo-substituted nucleobases are particularly pronounced[43]. As shown in the series of analogs 4-thiouridine[13], 2,4-dithiouridine[45], *arabino*-4-thiouridine[37], 3'-acetyl-4-thiothymidine[46], and co-crystalline 9-methyladenine:1-methyl-4-thiouracil[47], hydrogen bonding in nucleoside derivatives is determined by packing forces whereas a heterologous "inverse" Hoogsteen base pairing is present in the co-crystalline system (Fig. 9d). Since base pairs of the types shown in Figure 9 are generally found in co-crystalline samples whereas pure crystalline nucleosides do not exhibit any kind of uniform hydrogen bonds it can be assumed that the formation of heterologous base pairs dominates over packing forces but that the formation of homologous base pairs competes unsuccessfully[48].

The principal effect of base stacking on the stability of the structure of a helical nucleic acid complex becomes apparent on comparison of the properties of the homologous polymers polyuridylic acid [poly(uridine 5'-phosphate)], poly-U, and the 2-thio analog, poly-s^2U, in which uracil is replaced by 2-thiouracil. At low temperature, poly-U exhibits a double helical structure which "melts" to a single-stranded, coiled structure above 8°C; it can therefore form a complex with polyadenylic acid and function as a template in protein biosynthesis. In contrast, poly-s^2U forms a double-stranded helical complex with itself which is stable up to 68.5°C; this complex formation is favored to such a degree that poly-s^2U does not complex with poly-A and cannot be used in protein biosynthesis[49]. X-Ray diffraction studies on fiber samples of this material[50] have shown that its structure closely resembles that of A-DNA[51]. The nucleic acid strands adopt an antiparallel arrangement, thus leading to the base pair structure illustrated in Figure 10 with NH ··· S and NH ··· O hydrogen bonds.

The stability of the poly-s^2U helix cannot be due to the relatively weak N—H ··· S hydrogen bonding but must

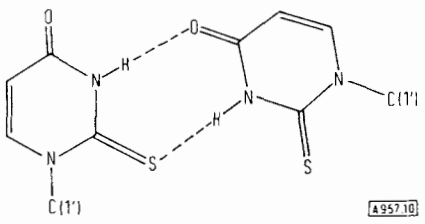


Fig. 10. Base pair in homopolymeric double-stranded helical poly-2-thiouridylic acid, poly-s^2U.

arise from stacking of the 2-thiouracil rings above one another with characteristic S(2)···N(1) interaction operating between neighboring nucleobases, similar to that found in the crystal structures of monomeric thiopyrimidine nucleoside derivatives[48]. Two effects tend to stabilize the helix: the readily polarizable thiocarbonyl groups can interact with the π-electron systems of adjacent 2-thiouracil groups, and in addition the relatively hydrophobic 2-thiouracil groups associate on helix formation in a hydrophobic linear region which is separated from the exterior medium, water, by the ribose phosphate chain[48].

4.3. Factors Determining the Conformation at the Glycosidic C(1′)—N Bond

NMR studies have shown that in solution nucleosides exist in a *syn-anti* equilibrium which lies almost exclusively on the side of the *anti* conformation in pyrimidine nucleosides but only predominately so in purine nucleosides[52,53]. The *syn* conformation can be forced by two kinds of effects: *inter*- and *intra*molecular forces.

4.3.1. *Inter*molecular Forces

On attachment of a nucleoside to a surface, whether to the active site of an enzyme, on incorporation into a double-stranded helical structure, or on crystallization, it has to adopt either the *syn* or the *anti* conformation. Which it actually adopts under these conditions cannot be predicted since intermolecular interactions such as hydrogen bonding forces, stacking effects, and general packing can play a crucial role.

As examples we can cite the purine nucleosides 3′-*O*-acetyladenosine[54], 6-thioinosine[55], 5′-deoxy-5′-methylammoniumadenosine[56], 2′-deoxyguanosine[57], formycin-HBr[58], adenosine 3′,5′-cyclophosphate[34], guanosine[59], inosine[59], and the pyrimidine derivatives 4-thiouridine[13], 2′-deoxy-2′-fluorouridine 3′,5′-diacetate[60], cytidine 2′,3′-cyclophosphate[35] obtained as crystals in the *syn* conformation. These purine nucleosides were all found to contain an *intra*molecular O(5′)—H···N(3) hydrogen bond providing additional stabilization for the *syn* conformation; 4-thiouridine however did not exhibit a potential *intra*molecular O(5′)—H···O(2) bond. On dissolution of this nucleoside, *syn-anti* equilibration occurs; as with all the other pyrimidine nucleosides, the equilibrium lies mainly on the *anti* side[61].

4.3.2. *Intra*molecular Forces

*Intra*molecular interactions can even stabilize the *syn* conformation in solution, as demonstrated by the nucleosides 8-bromoadenosine and 8-bromoguanosine[62] bearing a substituent adjacent to the glycosidic bond on the base component, and by N^1-β-D-ribosyl-6,7-dimethyllumazine[63], 6-methyluridine[64], and orotidine[53]. These molecules exist solely in the *syn* conformation since there is no room for the bulky substituents "above" the sugar ring.

However, these nucleosides thereby acquire an interesting property: their 5′-triphosphates cannot act as substrates for nucleotide polymerases[65,66]. This also means that the substrates for polymerases must be present in the *anti* conformation to be recognized by the active site so that reaction can ensue.

4.4. Mechanism of Action of the Enzyme Pancreatic Ribonuclease A

Pancreatic ribonuclease A specifically cleaves ribonucleic acids in such a manner that an intermediate pyrimidine 2′,3′-cyclophosphate is formed by transesterification. This cyclophosphate is further hydrolyzed to the 3′-phosphate. Both processes are reversible (Fig. 11).

Essentially two mechanisms have hitherto been discussed for the reaction of the pyrimidine 2′,3′-cyclophosphate with a nucleophile[67]: On the one hand the nucleophile can

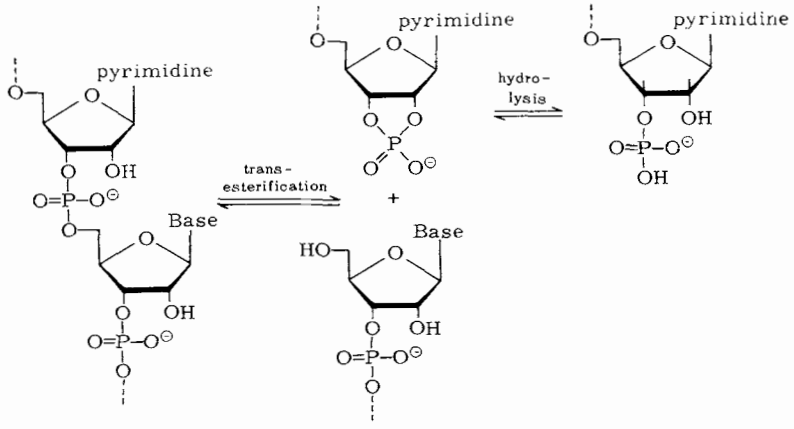


Fig. 11. Action mechanism of the enzyme pancreatic ribonuclease A.

attack the phosphorus atom on the side opposite the O(2') ester atom (in-line attack S_N2 mechanism), and on the other hand it can enter the vicinity of the O(2') atom (adjacent mechanism, the pyrimidine nucleoside 3'-phosphate arising *via* formation of an intermediate containing a pentacovalent phosphorus atom followed by pseudorotation of the five ligands).

4.5. Mechanism of Action of the Antileukemia Drug 6-Azauridine

6-Azauridine is an effective agent for the treatment of leukemia[7, 69]. Uridine kinase converts it *in vivo* into 6-azauridylic acid which inhibits the decarboxylation of orotidylic to uridylic acid by the enzyme orotidylic acid decarboxylase. The *de novo* synthesis of uridylic acid, and furthermore the synthesis of fresh RNA, is thus blocked (Fig. 13). X-Ray structure analysis of 6-azauridine-5'-phosphoric acid trihydrate (6-azauridylic acid) showed that this molecule, unlike all the nucleoside 5'-phosphates studied so far[21, 22], adopts the *gauche, trans*[70], and not the *gauche, gauche* conformation, about C(4')—C(5'). This unusual conformation is stabilized by electrostatic repulsion between the negatively charged nitrogen N(6) (0.42 unit charge) and the ester oxygen O(5')[71]. Just a small chemical, isoelectric modification thus has considerable stereochemical consequences. The positions of the phosphate groups in

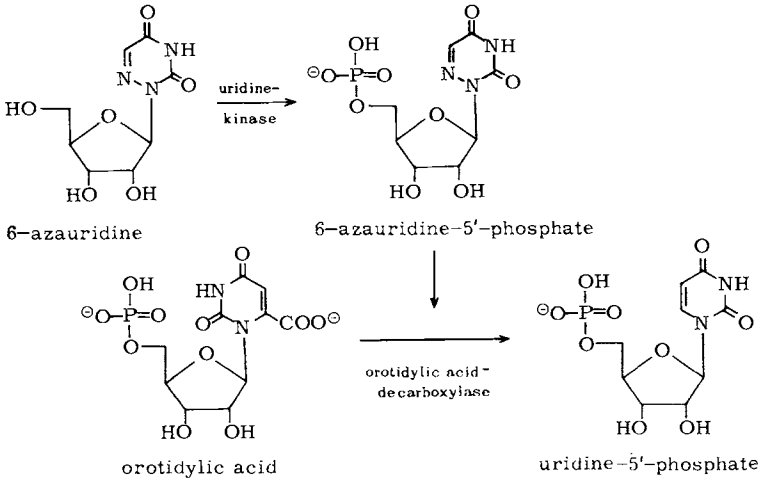


Fig. 13. Action mechanism of the antileukemia drug 6-azauridine.

In order to decide between the two mechanisms, the *endo* isomer of uridine 2',3'-cyclothiophosphate[18] was treated with pancreatic ribonuclease A in the presence of methanol as a nucleophile and the resulting methyl ester having an asymmetric phosphorus atom was isolated[68]. Thio-substituted uridine 2',3'-cyclophosphate had to be used in this experiment because the natural substrate cannot yield an asymmetric stereochemically defined reaction product.

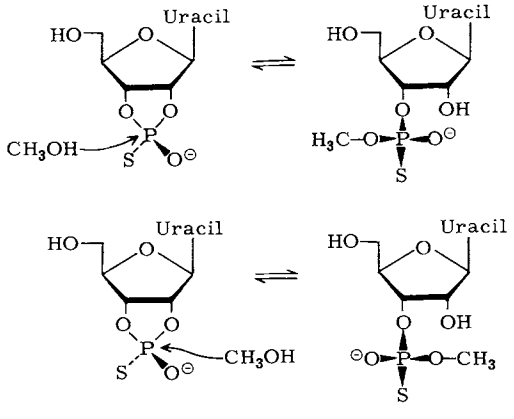


Fig. 12. Reaction of uridine 2',3'-cyclothiophosphate in methanol in the presence of ribonuclease A. The crystallographically determined structures of uridine 2',3'-cyclothiophosphate and the reaction product indicate occurrence of the in-line mechanism (S_N2). The adjacent mechanism would have yielded the isomeric product shown below.

The molecular structure of reactant and product, which were determined unequivocally by X-ray structural analysis, revealed that reaction had occurred by the in-line mechanism (S_N2)[68]. RNA is probably cleaved by pancreatic ribonuclease A in the same fashion.

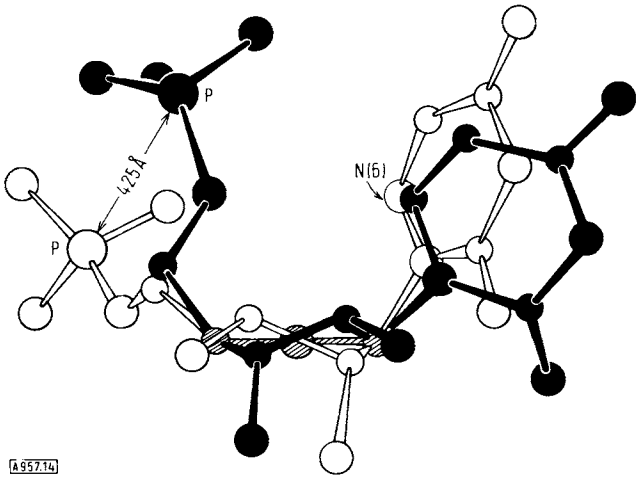


Fig. 14. Comparison of the structures of *gauche, gauche*-uridine 5'-phosphate (bold lines) and *gauche, trans*-6-azauridine 5'-phosphate. Interestingly, in addition to the phosphate group the atoms C(5') and N(1) also adopt differing positions as a result of the C(2')-*endo* and C(2')-*exo*—C(3')-*endo* sugar conformations (cf. also Fig. 6). The two molecules were drawn from crystallographic coordinates in such a way that the hatched atoms C(4')—O(1')—C(1') are common to both.

6-azauridylic acid and "normal" uridylic acid differ by 4.25 Å if the molecules are arranged such that the atoms C(4')—O(1')—C(1') are common to the two molecules (Fig. 14).

NMR studies[72] and X-ray structural analyses of analogous structures suggest that orotidylic acid will also have a *gauche, trans* conformation. Thus, the inhibition of the enzyme orotidylic acid decarboxylase can apparently be rationalized by binding of 6-azauridylic acid to the active site instead of the structurally similar orotidylic acid, thereby blocking the enzyme for metabolism of the true substrate.

Since the nucleoside 6-azauridine, which occurs in a *gauche, trans* conformation[71,72], also acts as substrate for the enzyme uridine kinase it appears that either this enzyme is not very specific, phosphorylating both *gauche, trans*-6-azauridine[71,72] and the "normal" *gauche, gauche*-uridine[72] at the 5'-hydroxyl group, or both substrates are fixed in a particular conformation on the surface of the active site and then undergo reaction.

4.6. Binding of Actinomycin D to DNA

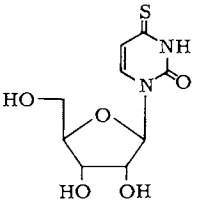
The antibiotic actinomycin D consists essentially of an aromatic phenoxazone chromophore linked to two peptide rings containing five amino acids each. The action of actinomycin D can be explained by its specific binding to DNA *via* G:C base pairs which interferes with readout of the information stored in the DNA[2]. As shown by X-ray structural analysis on a co-crystalline sample of actinomycin D and deoxyguanosine[73], one guanine is stacked above the phenoxazone ring and one below; the guanines can undergo hydrogen bonding with the peptide rings. Studies on models have demonstrated that actinomycin must be bound analogously to DNA: The phenoxazone chromophore inserts between consecutive G:C and C:G base pairs and hydrogen bonding takes place between guanine groups and the peptide rings of actinomycin D. Such a sequence-specific insertion does not distort the twofold symmetry of DNA mentioned above since actinomycin D itself has an approximately twofold axis[80].

4.7. Structures of the "Rare" Nucleosides 4-Thiouridine, Isopentenyladenine, Dihydrouridine

As adaptor molecules in protein biosynthesis, transfer ribonucleic acids (tRNA) mediate between messenger RNA, growing polypeptide chain, and amino acids yet to be incorporated[2,4–6,74,75]. Depending on their specificity they contain 70–85 nucleotides and are made up of double-stranded helical and single-stranded non-helical structural units. They contain about 10% of "rare" nucleosides such as 4-thiouridine, isopentenyladenosine, dihydrouridine, some of which are located at particular sites in the molecule and thus probably exert a structure- and specificity-determining effect.

4.7.1. 4-Thiouridine

Although it exists as the *anti* conformer in solution[61], 4-thiouridine crystallizes from water as the monohydrate in the unusual *syn* conformation[13] which is stabilized by crystal packing forces.

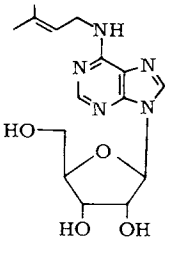


Co-crystalline samples of the 4-thiouridine analog 1-methyl-4-thiouracil and 9-methyladenine[41] prove to have "inverse" Hoogsteen-type base pairing with N(3)-U—H···N(7)A and N(6)A—H···O(2)U hydrogen bonds in which the sulfur atom does not participate. Moreover, this is the only base found so far in which purine and pyrimidine bases are stacked alternately in the crystal structure of the monomer.

Since the 4-thiouridine in *Escherichia coli* tRNA always occupies the same position, at a connection between two double-stranded helical regions[74], we may assume that it is incorporated to stabilize a particular tRNA structure by virtue of its conformational, base pairing, and base stacking properties, which differ from those of uridine.

4.7.2. Isopentenyladenine

The purine derivative N^6-(2-isopentenyl)adenosine is a component of the anticodon loop in a variety of tRNAs[74]. As was found in the crystal structures of N^6-(2-isopentenyl)-

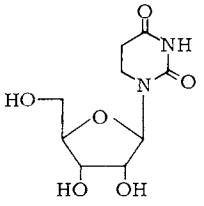


adenine[76] and N^6-(2-isopentenyl)-2-methylthioadenine[77], the isopentenyl groups project from the adenine ring in such a manner that the N(1) position is shielded and therefore inaccessible for Watson-Crick base pairing. This result supports the model concept that the anticodon loop should be single-stranded and devoid of base pairing so that messenger RNA can be read out by base pairing with the tRNA anticodon loop[78].

4.7.3. Dihydrouridine

Dihydrouridine crystallizes as the hemihydrate with two molecules in the asymmetric unit cell[79,80]. The molecules are in the *anti* conformation and the dihydrouracil group is not planar but in a half-chair conformation in both molecules. The conformation about the C(4')—C(5') bond is preferentially *gauche, trans* in both molecules. Having a non-

planar, nonaromatic base, dihydrouridine shows less tendency to participate in stacking than uridine. This factor, together with the preferred *gauche*, *trans* instead of



gauche, *gauche* conformation about the C(4')—C(5') bond, suggest the suitability of dihydrouridine for breaking a double-helix structure.

5. Conclusion

The first X-ray structural analyses of nucleotides were carried out with the aim of determining the structures of polymeric nucleic acids[81]. Although structural analyses on nucleic acids, which rely mainly on X-ray fiber diagrams of relatively low resolution, received considerable stimulus from the structural parameters determined for numerous nucleosides, nucleotides, and co-crystalline samples of base pairs, structural analysis of nucleic acid components has largely shaken off its model character. The reason is that nucleosides and nucleotides are *per se* biologically active units which can interact with enzymes. Thus a knowledge of the stereochemistry of the nucleosides and nucleotides permits conclusions to be drawn about the processes occurring at the active sites of enzymes.

The past four years have seen the preparation of single crystals of tRNA in several laboratories[75], and the first X-ray structure analysis of a tRNA was recently reported[82]. These structural studies will provide more details about the functional mechanism of tRNA and permit an insight into the conformation and the packing of the nucleotides in the polymer. Apart from the actinomycin-DNA complex[73] very little is known about the nature of nucleic acid-protein adduct formation. A research aim of the near future will be to prepare relevant co-crystalline samples to study these interactions which are of such paramount importance in biochemistry.

My own studies mentioned in this report are largely the fruits of the excellent cooperation that has taken place with Dr. P. C. Manor, Dr. S. K. Mazumdar, Dr. C. H. Schwalbe, Dr. D. Suck, and Miss U. Wittenberg, and of discussions with biochemists on the staff of this institute, to whom I am extremely grateful. I also wish to express my indebtedness to Prof. Dr. F. Cramer for his unfailing interest in structural problems and his support.

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Chemical Analysis of Synthetic Fibers[**]

By Dietmar Nissen, Volker Rossbach, and Helmut Zahn[*]

Dedicated to Professor Paul Schlack on the occasion of his 75th birthday

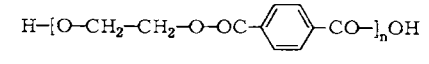
The analytical characterization of synthetic fibers has not kept pace with their development and production. Whereas the "second-generation" fibers have already conquered the market, the chemical investigation methods used until now for the three classical fiber polymers of the polyester, polyamide, and polyacrylonitrile types are still frequently unsatisfactory. Though they satisfy the requirements of production supervision and quality control, they do not supply enough information to enable us to understand and to explain the degradation of and damage to the polymers under hydrolytic, thermal, or thermooxidative influences. This report presents methods of chemical analysis that open up new possibilities for investigations of this nature on synthetic fibers. The results reported for commercial products must not be taken as an assessment of quality. They are simply intended to show the diversity to be expected in the chemical properties and to emphasize the practical basis of the chemical analysis of synthetic fibers.

1. Introduction

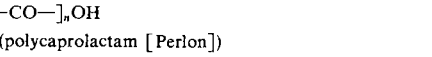
"One of the most frustrating problems in the early production of synthetic fibers was the inability to define polymer quality other than in terms of drawability and spinnability." This sentence from *Schlack*[1] shows how far it was necessary to come in order to reach the present position in the analytical characterization of synthetic fiber polymers[2, 3]. However, though a number of physical methods are now available, particularly for routine investigations, it is essential for synthetic fiber research to possess substantially complete and absolute numerical values for the chemical properties of the fibers, *i. e.* not simply comparison values such as are obtained in many test methods.

It appears from the literature[4] that fundamental new developments of fiber polymers are probably to be expected in the immediate future only to a limited extent and for special applications. In any case, the chemical modification of the three classical fiber polymers (Fig. 1) polyester, polyamide, and polyacrylonitrile is becoming increasingly important, and considerable problems are at the same time being raised for analytical chemistry. Methods from the analysis of natural macromolecules can help to solve these problems, as will be shown in the following discussion. Thus end group determination methods for polyesters and polyamides can be based on the well-known methods for the sequencing of proteins, such as the hydrazinolysis method of *Akabori*[6] and the dinitrophenylation technique of *Sanger*[7]. A method for the determination of acidic groups in cellulose by staining with methylene blue[8] can also be applied to the investigation of polyacrylonitrile, polyamide[9], and polyester[9, 9a, 14].

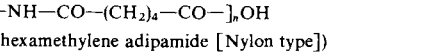
The polymers spun into filaments are not molecularly uniform substances, but contain a certain percentage of oligomers (polymer analogs having low molecular weights), which have proved valuable as model substances for the polymers, but have an adverse effect in the technical processing of the fibers. Analysis of the oligomers is therefore of great practical importance.



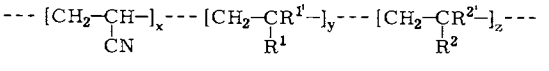
Polyester, PES (polyethylene terephthalate, PET [Terylene type])



Polyamide 6, PA 6 (polycaprolactam [Perlon])



Polyamide 6,6 (polyhexamethylene adipamide [Nylon type])



Polyacrylonitrile (modified), PAC

R^1, R^2 = various neutral, acidic, or basic groups; R^1, R^2 = alkyl or hydrogen

Fig. 1. Structural formulas of synthetic fiber polymers of the polyester, nylon, and polyacrylonitrile types [5].

The chemical characterization of commercial synthetic fibers also includes the investigation of any extraneous substances present, since these help to determine the processability of the fibers and their properties in use. However, the heterogeneity of these classes of substances, such as spinning oils, delustering agents, optical brighteners, light stabilizers, heat stabilizers, antistatics, and catalyst residues, makes both qualitative and quantitative determinations difficult, so that practically no generally valid, standardized analytical methods have been developed so far.

2. Determination of the Structural Units of Synthetic Fiber Polymers

Since the discovery of paper chromatography and later of thin layer chromatography, these methods have become

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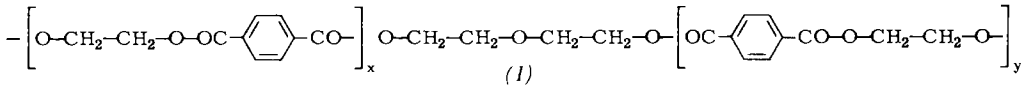
[**] Expanded version of a lecture to the 4th Textile Technical Forum, Schloss Elmau, 1972; 7th report in the series: Synthetic Fibers in the Wool Industry. 6th report: *W. L. Lindner*, Polymer *14*, 9 (1973).

essential aids in the analysis of synthetic fibers because of their ease of use. Once the polymer has been broken down into its monomeric units or their derivatives, these methods rapidly yield qualitative information on the composition of the macromolecules. Gas chromatography is also suitable for such routine determinations[10], and is also used for determination of the undesirable diethylene glycol structure [middle part of *(1)*] in polyethylene terephthalate[11].



(1)

Besides paper chromatography and thin layer chromatography, which have been in use for some time for the determination of the structural units of commercial nylon[12], polyurethane[12], and polyester[13], paper electrophoresis, which has been recommended for the analysis of hydrolysis products of nylons[13], has also proved useful in the qualitative determination of the monomer units of copolyesters[14] (Fig. 2).

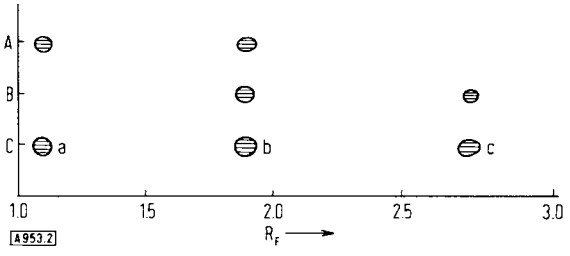
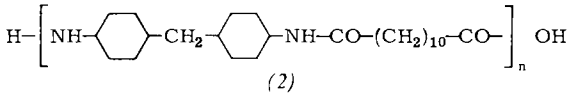


Fig. 2. Electropherogram of HCl hydrolysis products of modified polyester fibers (reference substance for the R_f values: Neucoccin [C. I. 16255]). A) Unitika copolyether ester, B) DuPont Dacron 65, C) reference substances (a: *p*-(β-hydroxyethoxy)benzoic acid, b: terephthalic acid, c: 5-sulfoisophthalic acid).

By thin layer chromatography of hydrolysis products of the silk-like Qiana fibers, it is possible to show with the aid of reference substances that this product is the polyamide of bis(4-aminocyclohexyl)methane and *n*-decanedicarboxylic acid *(2)*[15].

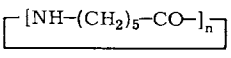


(2)

On the other hand, the structural units of copolymers of acrylonitrile cannot be determined by this simple method, since the paraffinic polymer chain (Fig. 1) cannot be hydrolyzed.

3. Importance of the Oligomers to the Analysis of Synthetic Fibers

As early as 1925, *Staudinger* and *Lüthy*[16] described the isolation of methyloligooxymethylene methyl ethers (CH_3—[OCH_2—]$_n$$OCH_3$; $n = 1$ to 14) and acetyloligooxymethylene acetates (CH_3CO—[OCH_2—]$_n$$OCOCH_3$; $n = 1$ to 20), though the molecular homogeneity of these substances was difficult to check by the means available at that time. This opened up a field of research whose importance was underlined by *Carothers*[17] in 1930 in his suggestion that low molecular weight homologs be isolated from synthetic polymers for chemical and physical structural investigations aimed at obtaining an understanding of the high polymers. Nine years later, *Schlack* and *Kunz*[18] extracted the cyclic dimer *(3)* and trimer *(4)* as well as monomeric lactam from caprolactam polymers.



(3), n = 2
(4), n = 3

Attempts made between then and 1967 to synthesize polymers with definite chain lengths or ring sizes from the monomers to allow the study of changes in the physical and chemical properties with increasing degree of polymerization have been reviewed by *Heidemann*[19].

To avoid the difficulties associated with the direct synthesis of oligomers, repeated efforts were made to obtain the pure oligomers by fractionation of the extract from the polymers[20], since the formation of oligomers is a phenomenon that accompanies melt condensation in particular, and oligomers can therefore be easily isolated from such polymers[19] as "natural", though usually undesirable, components. The most important of the fiber-forming polymers produced by melt condensation are the nylons and polyesters.

The specific synthesis of oligomers with degrees of polymerization greater than 8 is difficult if not impossible by conventional methods, not only because of solubility factors. As a result of incomplete reaction, costly purification of the resulting mixture is necessary in every case[21,22]. This is also the case when the Merrifield technique[23] is used for the preparation of higher linear polyamide and ethylene terephthalate oligomers, *i.e.* the purity of the products is usually unsatisfactory[24-26], which agrees with experience in peptide chemistry. In the preparation of acrylic acid oligomers, the use of molecularly uniform phenol-formaldehyde condensates as a template should help to provide definite products[27].

Following the remarkable successes of *Rothe et al.*[24], *Kusch*[25], *Repin*[28], and *Pénisson*[29] in the synthesis of higher linear and cyclic oligomers of the nylon 6, nylon 6,6, and ethylene terephthalate series, it can nowadays be said that for most purposes, oligomers with degrees of polymerization of less than 10 are quite satisfactory as model substances for the polymers. Thus from the heptamer upward, the dimethyl esters of polyethylene terephthalate do not differ from the polymer in their solubility, melting point, X-ray powder pattern, or IR spectrum[29]. In the nylon 6,6 series, X-ray studies show the same super-

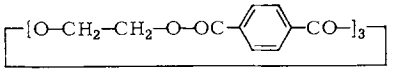
structure for the tetramer and pentamer as for the polymer[30].

An important objective of oligomer research has thus been achieved, namely the provision of substances for model reactions in which the molecular uniformity of the compounds ensures a simpler situation than in the case of an unfractionated polymer. Oligomers with degrees of polymerization of less than 10 are adequate for this purpose, and have already been used in many cases (Table 1).

Table 1. Scalar properties of polymers, investigated with oligomers as model substances [19, 31].

Melting point
Viscosity
UV and IR absorption
Crystallinity and conformation (X-ray studies, IR and NMR spectroscopy, density measurements)
Influence of chain length and structure on a covalently bonded chromophore (2,4-dinitrophenyl, 4-nitro-1-naphthyl residue) [32, 33]
Dyeing mechanism (crystalline ponceau 6R [C.I. 44], 2,4-dinitro-1-fluorobenzene, disperse dyes)
Absorption of moisture
Rate of hydrolysis
Photostability [34]
Thermostability [34, 35]

Interest is now being focused mainly on the manner in which the oligomers are formed and on their behavior in the production and processing of fiber-forming polymers. Thus the difficulties encountered in the processing (spinning, texturing, dyeing) of polyethylene terephthalate, which are caused by the escape mainly of the cyclic trimer *(5)* from the fiber, have led even recently to investigations



(5)

having practical aspects[36, 37]. These investigations are greatly facilitated by the model substances. Attempts have recently been made to decrease the content of oligomer by extraction of the granulated polymer before spinning in order to obtain polyester filaments with better properties for HT (high-temperature) dyeing[38].

Table 2. Analytical characterization of Qiana oligomers [15].

	Linear pentamer		Cyclic monomer	
Mol. wt.	calc. 2038 exp. 2050		substance insoluble	
Elemental analysis	C	H	C	H
	calc. 73.60	10.90	74.25	10.89
	exp. 73.40	11.18	74.18	11.11
	N	O	N	O
	calc. 6.87	8.63	6.92	7.9
	exp. 7.23	8.30	6.92	7.7
R_f value	0.96 [a] 0.0 [b]		0.83 [a] 0.94 [b]	
M.p.	220 °C		> 350 °C (sublimable)	

[a] Eluent: 2-butanol/formic acid/acetic acid/water [22].
[b] Eluent: tetrahydrofuran/cyclohexane/water [39].

With the continuous development of new homopolymer and copolymer synthetic fibers, the need to prepare suitable oligomers for their analytical investigation will continue in the future. Table 2 shows the results of attempts to isolate oligomers from Qiana poly[(4,4'-methylenedicyclohexyl)dodecanamide] *(2)*[15].

4. Determination of the Functional Groups of Polyesters, Nylons, and Polyacrylonitrile

The functional groups (—OH, —COOH, —SO_3H, —OSO_3H, —NH_2, —CN) of the three fiber polymers polyester, nylon, and polyacrylonitrile and of the modified types derived from them are of great importance to their processability and to their properties in use, and play a crucial part in cases of damage. The specific determination of these groups is therefore important for the evaluation of a polymer and the detection of changes due to external influences such as hydrolysis, thermolysis, thermal oxidation, and irradiation.

4.1. Determination of Acidic Groups

4.1.1. Carboxyl End Groups of Polyesters

The reason why every polyethylene terephthalate (PET, polyesters of the Terylene type) contains carboxyl end groups as well as the hydroxyl groups resulting from the synthesis method is the thermal cleavage of the polymer chains due to the relatively high polycondensation temperatures and the residence times required to obtain high molecular weights[40–42]. The resulting ratio of hydroxyl to carboxyl groups provides a measure for the assessment of the chemical quality of the polyester[43]. Thus hydroxyl groups are particularly important to the thermal stability of polyesters[44, 45], since, as long as there are free hydroxyl end groups present in the molten polymer, the vinyl ester groups that are formed together with carboxyl groups on chain scission are transesterified with formation of a new polyester linkage[44]. A carboxyl group is thus formed at the expense of a hydroxyl group, but the average degree of polymerization has not decreased. On heat treatment of fibers below the melting point between 180 and 220 C, on the other hand, an increase in molecular weight occurs with consumption of both types of end groups[33, 46, 47].

The content of carboxyl groups is an important factor in connection with the susceptibility to hydrolysis[48], since these end groups have a catalytic effect in this process[46]. Their number can be increased by hydrolytic[49] or photolytic[50, 51] damage and by thermal oxidation[52, 53].

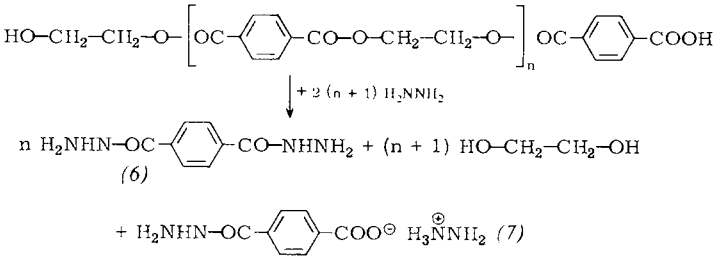
The determination of carboxyl end groups in PET is thus not only important for the determination of the number average molecular weight, but also serves for the elucidation of damage to the polymer by hydrolysis, heat, and light. In view of this fact, it seems peculiar that acidimetric titration is still the most commonly used method for the determination of carboxyl groups in PET, with addition of an indicator for visual end point determination[54] or with photometric[55], potentiometric[56], or conductomet-

ric[57] end point determination, since titration methods are not specific for end groups and can give reasonably reliable results only up to an average molecular weight of 20000. Above this limit, the ratio of the end groups (which are present in very small concentrations) to frequently unidentifiable impurities that interfere with the titration becomes increasingly unfavorable. This disadvantage cannot be overcome by the use of larger polymer samples and dilution of the titrant[58].

Chemical methods have also been described for the determination of carboxyl end groups in aliphatic polyesters, but these have not been used for PET. The conversion of the carboxyl groups into methyl ester groups by reaction with diazomethane should allow the determination of carboxyl groups by a methoxyl group analysis[59]. Alternatively, these groups may be allowed to react with phenyl isocyanate in the presence of pyridine. The resulting anilide end groups are determined by hydrolysis and photometric determination of the aniline formed[60].

4.1.1.1. Principles of the Determination of Carboxyl End Groups by Hydrazinolysis

A new possibility for the chemical determination of carboxyl groups in PET is offered by the application of the principle developed by *Akabori et al.*[6], according to which C-terminal amino acids in proteins are determined by hydrazinolysis[33]. The hydrazinolytic degradation of PET, which proceeds readily, has already been used for a wide range of purposes, *e.g.* for the separation of PET from mixtures with wool[61], for the investigation of the harmful action of organic bases on PET fibers[62], for the determination of the degree of crosslinking of cured polyester resins[63], and for the determination of methyl ester groups and diethylene glycol groupings in PET[11,43,64]. However, no analytical use has so far been made of the fact that the reaction of hydrazine with PET leads to quantitative cleavage of ester linkages in the polymer, with liberation of terephthalomonohydrazide *(7)* as the hydrazinium salt from C-terminal[*] terephthalic acid units, together with large quantities of terephthalodihydrazide *(6)* as the main product. The monohydrazide can be separated from the reaction mixture by ion exchange (Fig. 3) and determined photometrically.



The polyester material is allowed to react for five hours at 70 °C with 250 times as much of a hydrazine/dioxane/*n*-butanol mixture (15:70:15). The hydrazinolysis mixture is evaporated and then extracted with water. The extraction solution is discontinuously adsorbed on QAE Sephadex A-25 ion exchanger, which is then washed with water. The adsorbed terephthalomonohydrazide is desorbed with a measured elution volume of 0.1 N hydrochloric acid and determined photometrically at the absorption maximum of 240 nm. The content of carboxyl end groups is found from a calibration curve plotted for synthesized terephthalomonohydrazide.

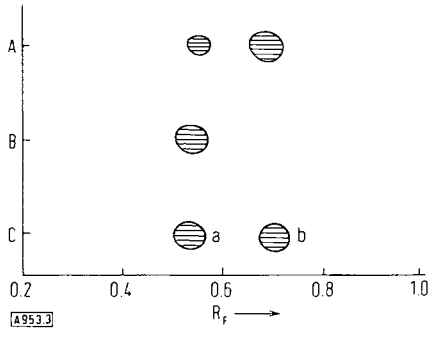


Fig. 3. Thin layer chromatogram of the hydrazinolysis products of a polyethylene terephthalate. A = before ion exchange; B = after ion exchange; C = reference substances (a: terephthalomonohydrazide *(7)*, b: terephthalodihydrazide *(6)*). Silica gel HF 254 (Merck, Darmstadt, Germany); dioxane/ammonia (25%)/water (65:8:27).

Under these analytical conditions, the reaction of PET with hydrazine proceeds uniformly and does not lead to the formation of secondary hydrazides, which could be formed at higher temperatures if the excess of reagent is too small[65].

4.1.1.2. Application of Hydrazinolysis

The contents of carboxyl end groups found for polyethylene terephthalate fibers are between 20 and 59 meq/kg of fiber, depending on the manufacturer and the type of fiber (Table 3); these values agree with recent literature data[45,66].

Table 3. Content of carboxyl end groups in commercial polyethylene terephthalate fibers.

Producer, trade name, degree of delustering [a]	COOH [meq/kg] Hydrazinolysis method [b]	Colorimetric indicator method [c]
ICI Terylene W11, gl	32	---
ICI Terylene W16, hm	37	37
Enka Diolen, gl	40	64
Enka Diolen FL, gl	59	56
Hoechst Trevira 220, gl	20	20
Hoechst Trevira 220, mt	22	34
Hoechst Trevira 550, mt [d]	17	13
Hoechst Trevira 560, mt [d]	21	16
Rhodiaceta Tergal, hm	25	---
Rhodiaceta Tergal, mt	26	35

[a] gl = bright, hm = semi-dull, mt = dull.
[b] Coefficient of variation = 9.5%; confidence belt = ±2.0 meq/kg (for 95% statistical certainty).
[c] Coefficient of variation = 7.5%; confidence belt = ±2.0 meq/kg (for 95% statistical certainty).
[d] Chemically modified polyester high-shrinkage fibers.

The results are compared with values obtained by a colorimetric indicator method. The principle of this method was used by *Hensley*[67] for the determination of traces

[*] In this connection the term "C-terminal" means carboxyl terminal.

of acid in dimethyl terephthalate. In analogy with this method, the color reaction between the indicator bromophenol blue in its anionic form and the carboxyl groups is used for the quantitative photometric determination of the latter in PET. The decrease in the blue color is proportional to the number of equivalents of acid present in the solution.

The inadequacy of this non-specific method can be seen on comparison of the results (Table 3) with those obtained by hydrazinolysis. The differences which are sometimes pronounced are due to the fact that ionic fiber additives do not interfere with the end-group-specific formation of terephthalomonohydrazide *(7)* and its detection, whereas they can influence the color change of the indicator. Similar differences are also found in the determination of amino end groups in nylon fibers by titration on the one hand and by dinitrophenylation on the other (Table 7).

4.1.2. Carboxyl End Groups of Nylons

The carboxyl groups of nylons are partly responsible for the net charge of these polymers, and hence, according to *Zollinger*[68], influence their dyeability by acidic dyes. They are mainly determined by titration in benzyl alcohol according to *Waltz* and *Taylor*[69] in many variants[70]. The end point is determined conductometrically, potentiometrically, or visually with color indicators. Because of the high dissolution temperature of nylons in benzyl alcohol (approx. 160 °C), considerable quantities of benzoic acid are formed during the analysis. Attempts have been made to eliminate this methodical error by very precise standardization of the analytical conditions. Other solvents described for the determination of carboxyl groups, such as 2,2,2-trifluoroethanol[71, 72] and β-phenylethanol[73], have only occasionally been used.

In *Pätzold*'s method[72], the nylons dissolved in trifluoroethanol are titrated conductometrically with aqueous sodium hydroxide solution. As in the acidimetric titration in benzyl alcohol[69], the graphical determination of the equivalence point in this method leads to unsatisfactory results. On the other hand, definite reproducible values are obtained by mathematical evaluation, in which the regression lines for both branches of the titration curve are determined, the transition section being disregarded, and the intersection is determined mathematically.

In this way, carboxyl group contents of 50 to 68 meq/kg, depending on the manufacturer and the intended use, are found for a number of commercial nylon fibers (Table 7).

The titrimetric determination of the carboxyl end groups is more problematic than that of the amino end groups, owing to the lack of suitable solvents for nylons. Nevertheless, only one method for the specific chemical determination of carboxyl end groups has been reported in the literature. *Staudinger* and *Schnell*[74] esterified the carboxyl groups in the heterogeneous phase with a solution of diazomethane in ether and determined the methoxyl content by the Zeisel method. This method has also been used more recently[75]. As was shown by *Smith*[76], however, 25% of the carboxyl groups remain unesterified even after reaction for seven days.

The reaction in the homogeneous phase in the system calcium chloride/methanol/acetic anhydride, based on a method given by *Blackburn* and *Phillips*[77] for the methyl esterification of wool, also leads to only 58% reaction of the carboxyl groups[32].

4.1.3. Acidic Groups of Polyacrylonitrile

The acidic groups in polyacrylonitrile fibers may be strongly acidic sulfo or sulfate groups and weakly acidic carboxyl groups. The sulfo groups constitute about 80% of the total content of strongly acidic groups[78]. They are introduced into the polymer either by the catalyst as end groups[79] (reactions (a)—(d)) or with comonomers (Fig. 4) that are polymerized into the polyacrylonitrile[80] or grafted onto the preformed polymer[81]. Carboxyl groups can also be formed by hydrolysis of nitrile and other groups during polymerization[83, 84] or processing[85].

Radical generation

$$KO{-}SO_2{-}O{-}O{-}SO_2{-}OK \rightarrow 2\,{}^{\cdot}O{-}SO_2{-}OK \quad (a)$$

$$KO{-}SO_2{-}O{-}O{-}SO_2{-}OK \rightarrow O_2 + 2\,{}^{\cdot}SO_2{-}OK$$

$$KO{-}SO_2{-}O{-}O{-}SO_2{-}OK + Fe^{2+} \rightarrow KO{-}SO_2{-}O^- + KO{-}SO_2{-}O^{\cdot} + Fe^{3+} \quad (b)$$

Initiation

$$KO{-}SO_2^{\cdot} + H_2C{=}CH{-}CN \rightarrow KO{-}SO_2{-}CH_2{-}\dot{C}H{-}CN \quad (c)$$

$$KO{-}SO_2{-}O^{\cdot} + H_2C{=}CH{-}CN \rightarrow KO{-}SO_2{-}O{-}CH_2{-}\dot{C}H{-}CN \quad (d)$$

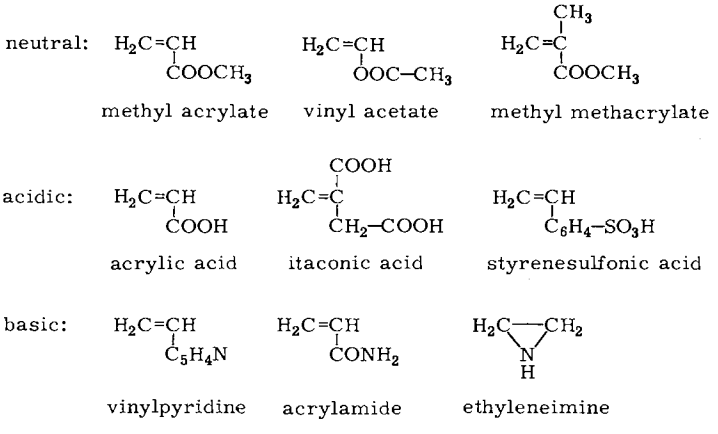


Fig. 4. Typical comonomers for the preparation of polyacrylonitrile fibers [80, 82].

Beckmann and *Glenz*[86] were the first to carry out quantitative determinations of acidic groups in acrylonitrile polymers by titration. *Kirby* and *Baldwin*[83] later showed that the values obtained are too low. These authors developed a method in which the strongly acidic groups and the weakly acidic groups can be determined separately by potentiometric titration. However, since many of the acidic groups are present in the polymer as salts, an ion exchange must be carried out before the titration.

The sulfonate and sulfate groups can also be determined by IR spectroscopy[87]; however, this method requires a difficult calibration with radioactive sodium.

Hilden[88–90] describes a simple determination of the acidic groups of polyacrylonitrile, in which the polymer is dyed

with methylene blue [C.I. 52015], a basic dye that was used earlier for the investigation of fiber damage in polyacrylonitrile[91]. The fibers are dyed in the heterogeneous phase at various pH values to achieve selective bonding of the dye to the strongly acidic groups in the acidic range and to the strongly acidic and weakly acidic groups in the neutral range: the content of weakly acidic groups can then be calculated by difference. Table 4 shows the results obtained in this way for a series of commercial polyacrylonitrile fibers.

Table 4. Determination of acidic groups in commercial polyacrylonitrile fibers by dyeing with methylene blue [88].

Producer, trade name	Acid groups [meq/kg] strongly acidic [a]	strongly acidic weakly acidic [b]
Bayer Dralon	57	63
Bayer Dralon bifilar	53	59
DuPont Orlon 42	67	74
DuPont Orlon 74	1	2
DuPont Orlon 75	69	76
DuPont Orlon 75 B	67	75
Phrix Redon F	58	62

[a] Dyeing at pH 1.6.
[b] Dyeing at pH 6.5.

Apart from the fact that the heterogeneous reaction makes quantitative dye saturation of the functional groups problematic[92], since the accessibility of these groups depends on the temperature, the fine structure of the fiber[86,93], and the ion distribution[92], the determination of the weakly acidic groups is also difficult for other reasons. Whereas the bonding of the dye to the strongly acidic groups is partly covalent in character[94], the dye molecules bonded by the weakly acidic groups partly dissociate again during the extraction for the removal of unbound dye. The values for the strongly acidic groups thus agree with other literature data[83], whereas those for the weakly acidic groups are considerably lower.

4.2. Determination of the Basic End Groups of Nylons

In the analysis of nylons, the determination of the basic groups, which are generally referred to simply as amino groups, is more important than that of the carboxyl groups, since the content of basic groups determines the ability of the fibers to be dyed with reactive, acidic, and 2:1 metal complex dyes[93,95,96], and is also important for the recognition of fiber damage due to acids[97], heat[98], or light[99]. The basic end groups are mainly determined in practice by photometric or conductometric titration or by titration with the addition of color indicators[100]. What was said about the titrimetric determination of carboxyl groups in polyesters is also applicable to these analytical methods: they are non-specific, and so do not allow a differentiation between basic end groups and other basic groups (total basicity).

Despite the growing importance of the analysis of basic end groups, particularly for newly developed special end-group modified or copolymerized nylons (Fig. 5)[101–103], only a few chemical determination methods are to be found in the literature.

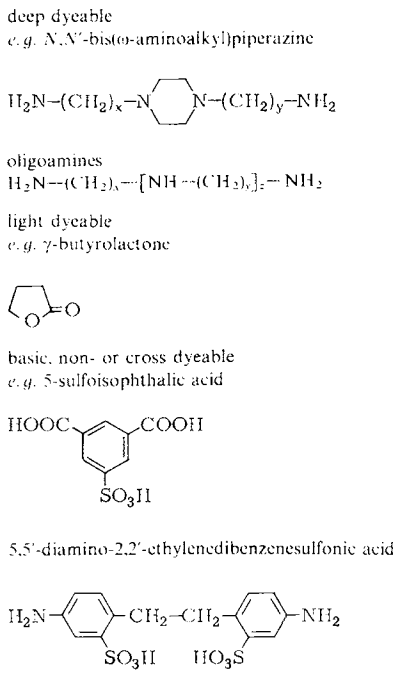


Fig. 5. Modifying components for the production of nylon fibers with modified dyeability [101–103].

A qualitative method is based on the ninhydrin reaction[104]. *Richter et al.*[105] developed a quantitative method, which should be particularly suitable for the determination of low contents of primary amino end groups, and which involves reaction with succindialdehyde to form pyrrolyl end groups, which are then determined colorimetrically by the Ehrlich reaction. 2,4-Dinitro-1-fluorobenzene (DNFB) is the reagent most commonly used for the chemical determination of amino end groups.

4.2.1. Principles of the Dinitrophenylation of Nylons

As early as 1953, one of us and *Rathgeber*[98] dinitrophenylated nylon 6 (Fig. 6) and nylon 6,6 by a procedure taken from wool analysis[106].

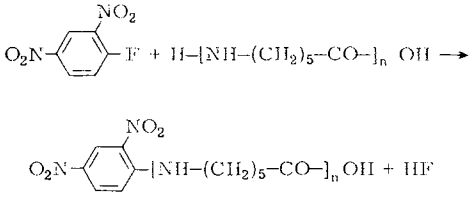


Fig. 6. Reaction of nylon 6 with 2,4-dinitro-1-fluorobenzene (DNFB).

However, structure-dependent errors have been detected in this method[107,108]. Thus since the diffusion of the reagent is rate-determining in the heterogeneous phase, fine-structure parameters such as the degree of orientation of the fibers influence the accessibility and reaction of the amino groups (Fig. 7).

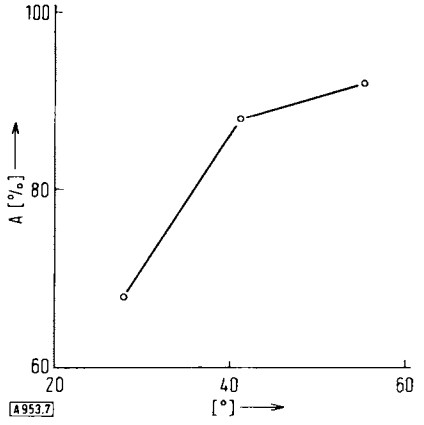


Fig. 7. Proportion A of amino groups that can be dinitrophenylated with 2,4-dinitro-1-fluorobenzene in nylon 6 fibers with different degrees of orientation. Abscissa: azimuthal half widths of the 020 reflection as a measure of the degree of orientation of the fibers.

Garmon and *Gibson*[109] therefore carried out the dinitrophenylation in the homogeneous phase with a very large excess of reagent, with the result that the photometric determination of the dinitrophenylated end groups becomes inaccurate. These authors also failed to consider that the total basicity and the content of amino groups may be different in commercial nylon fibers. Basic fiber additives may react with DNFB, a fact that must be disregarded in this method, which also allows no differentiation between different dinitrophenylatable groups such as primary and secondary amino groups and amidine groups.

Dinitrophenylation in the homogeneous phase in the system 2,2,2-trifluoroethanol/sodium hydrogen carbonate/water[32,110] eliminates these difficulties and also allows a differentiation between the basic end groups mentioned.

The nylon is dissolved in a 1.7% solution of DNFB in 2,2,2-trifluoroethanol (nylon concentration: 1%), and 5% aqueous sodium hydrogen carbonate solution is added (6%). After 14 hours the DNP-nylon (DNP=2,4-dinitrophenyl) is precipitated with 10 times as much water at pH 3, freed from adhering reagent by extraction with ethyl acetate, and dried. The DNP-nylon is then dissolved in trifluoroethanol and determined photometrically at the 350 nm absorption maximum. The content of amino end groups is determined from a calibration curve plotted for DNP-oligomers from the nylon 6 and nylon 6,6 series, for which the chromophore has been found to be independent of the structure.

A DNFB-catalyzed condensation of the amino and carboxyl groups such as was observed by *Heikens et al.*[111] for ε-aminocaproic acid in an ethanol-water mixture containing hydrogen carbonate takes place only to a very small extent in this model substance under the above analytical conditions (content of DNP-ε-aminocaproyl-ε-aminocaproic acid $\leqslant 5$ mol-%). This is probably due to the large excess of reagent.

Since the activation parameters of the dinitrophenylation for ε-aminocaproic acid and for the polymer have been found to agree (Table 5), so that the "principle of equal reactivity"[112,113] is satisfied, a condensation can also be ruled out for the polymer. Thus in the dinitrophenylation of nylon, no amino groups are lost by side reactions.

Table 5. Activation parameters, determined according to the Eyring theory of the activated complex, for the dinitrophenylation of ε-aminocaproic acid and nylon 6 at 30 °C.

	ΔH^* [kcal/mol]	ΔG^* [kcal/mol]	ΔS^* [cal deg^{-1} mol^{-1}]
ε-Aminocaproic acid	15.0	22.6	−23.9
Nylon 6	16.7	23.1	−20.2

No molecular weight fractionation occurs in the isolation of the DNP-nylon, as is shown by the correlation of the values obtained with those found potentiometrically[69] in the molecular weight range between 6000 and 18000 (Table 6). If the analytical conditions are adhered to, the dinitrophenylation proceeds quantitatively, as difference analyses by the method of *Richter et al.*[105] have shown.

Table 6. Determination of the basic groups of nylon 6 (without added regulators) [a] by potentiometry [69] and by dinitrophenylation.

$\bar{M}_n$	Basic groups [meq/kg]	
	Potentiometry	DNP method
17500	58	54
14000	72	67
12200	82	77
9000	110	101
6300	160	147

[a] These products were kindly made and characterized for us by BASF, Ludwigshafen.

4.2.2. Use of Dinitrophenylation

4.2.2.1. Determination of Primary Amino Groups

Amino group contents of between 26 and 65 meq/kg of fiber have been found for commercial fibers of the nylon 6 and nylon 6,6 types, depending on the manufacturer and the intended use (Table 7).

End group equivalence of the free and acylated amino groups to the carboxyl groups has been found for unbranched polycaprolactam[115]. This is confirmed by the complete end group analysis of nylon 6 fibers (Table 7), but only if the total amino group content is calculated from the dinitrophenylation values and compared with the content of carboxyl groups found conductometrically. Alkalimetric titration usually gives excessively high contents of amino groups because of its non-specificity. This also explains why the number average molecular weights calculated from the dinitrophenylation values are higher than the values given in the literature[116] or at the upper limit of the range[117], since the latter were all determined by titrimetric methods.

For a complete end group analysis, the acylated amino groups must also be determined. The acyl residues are derived from monofunctional carboxylic acids (acetic acid, propionic acid, benzoic acid) added to the nylon 6 and nylon 6,6 polymerization mixtures as molecular weight stabilizers. Because of these regulators, equivalence of the free end groups cannot be expected in technical nylon.

A method is described in the literature for the determination of the acetyl residues[118,119], in which the acetic

Table 7. End group content and molecular weight ($\bar{M}_n$) of commercial nylon fibers.

Producer, trade name	[η] [114] [dl/g]	Basic groups [meq/kg] DNP method	Potentiometry [69]	R—CO—NH [meq/kg] [a]	COOH [meq/kg] Conducto-metry [72]	$\bar{M}_n$
Enka Perlon	1.05	49	70	6	53	18500
Bayer Perlon	1.07	25	23	26	50	19800
Phrix Perlon	0.92	40	51	18	53	18000
Emser-Werke Grilon	1.09	36	42	17	57	18200
Rhodiaceta Nylon	1.07	45	46	26	54	16000
Monsanto Nylon		65 (prim.) ≥ 3 (sec.)	not titratable	11	68	13500

Reproducibility of the methods used

Method	Variation coefficient [%]	Confidence belt (for 95% statistical certainty) [meq/kg]
DNP method	2.7	±0.9
Acetyl determination	15.4	±4.8
Conductometry	4.0	±2.7

[a] R = CH_3, C_2H_5, C_6H_5.

acid liberated by phosphoric acid is distilled azeotropically with xylene and then titrated. The following procedure[32] is simpler. The nylon is digested with 50% sulfuric acid, and the organic acids are steam distilled and then titrated potentiometrically. The pK value gives an indication of the acid present.

Though this method has a fairly high coefficient of variation (Table 7), the statement by *Dinse* and *Praeger*[118] that microanalytical or semimicroanalytical acetyl determinations on nylons are impossible does not appear to be justified.

4.2.2.2. Determination of Secondary Amino Groups and Detection of Amidine Groups

McIntire et al.[120], in 1953, described the possibility of differentiating between primary and secondary amines by dinitrophenylation, since the absorption maximum of the primary DNP-amine at 350 nm is displaced to 390 nm for secondary DNP-amine (Fig. 8).

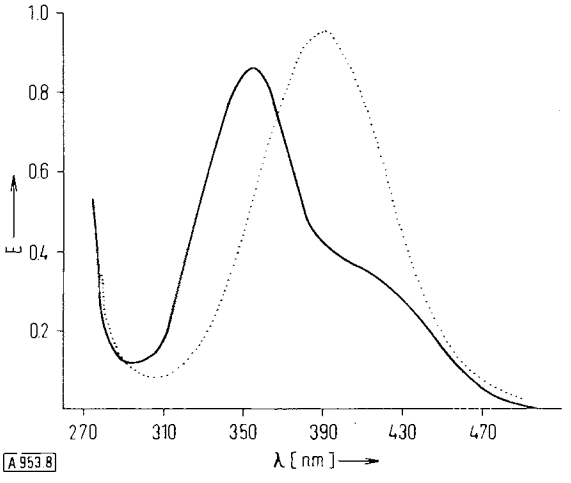


Fig. 8. Spectra of dinitrophenyl-*n*-propylamine (—) and dinitrophenyl-di-*n*-propylamine (····) in 2,2,2-trifluoroethanol ($c = 5.1 \times 10^{-5}$ mol/l).

The spectra of a large number of dinitrophenylated primary and secondary amines show that when the alkyl residue H—$[CH_2—]_n$ has a chain length of $n > 1$, the chromophore absorbs independently of the structure of the rest of the molecule.

The presence of secondary amino groups can therefore be deduced from the extinction ratio E^{350}/E^{390} of a dinitrophenylated polyamide. The spectral behavior is evaluated for the quantitative determination of primary and secondary amino groups in polymers by a two-component analysis developed on the basis of measurements on DNP-monoalkylamines and DNP-dialkylamines.

$c_1 = (7.49 \times E^{350} - 3.62 \times E^{390}) \times 10^{-5}$ mol/l

$c_2 = (7.21 \times E^{390} - 3.41 \times E^{350}) \times 10^{-5}$ mol/l

c_1, c_2 = concentration of primary and secondary amino groups

E^{350}, E^{390} = extinctions at 350 and 390 nm

In addition to many other products that are formed by the action of heat on aliphatic polyamides, particularly in the presence of oxygen, a number of primary and secondary amines, amino acids, and other compounds containing nitrogen, which should react with DNFB because of their structure, have been described[121–123]. However, since it has been necessary until now to liberate and isolate these substances by hydrolysis in order to detect them, there are only a few known groupings that are formed in the polymer during thermal degradation and can be dinitrophenylated there. *Kamerbeek et al.*[124] showed that in nylon 6 and nylon 6,6 at high temperatures, two amino end groups react with elimination of ammonia, so that a secondary amino group is formed with chain doubling.

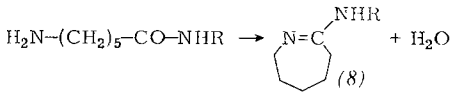
$2\ R—NH_2 \rightarrow R—NH—R + NH_3$

R = HO—$[CO—(CH_2)_5—NH—]_n$CO—$(CH_2)_5$ or

HO—$[CO—(CH_2)_4—CO—NH—(CH_2)_6—NH—]_n$CO—$(CH_2)_4$—CO—NH—$(CH_2)_6$

In NMR studies on the gelation of nylon 6 and nylon 6,6, secondary and tertiary amino groups were recently detected in the polymer itself[125].

There is also a possibility that nylon 6 contains the semicyclic amidines of the type *(8)* postulated by *Schlack*[126], though these have not yet been directly detected.

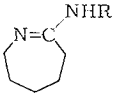


(8)

R = HO–[CO–$(CH_2)_5$–NH–]$_n$ CO–$(CH_2)_5$

For nylon 6,6, a reaction between the cyclopentanone Schiff bases mentioned by *Wiloth*[127] and DNFB must be considered, and dinitrophenylation of the pyridines detected by *Goodman*[128] is also possible. All these basic groups are included in the results of titrimetric determinations, and are generally referred to simply as amino groups, despite their different p*K* values.

2-Benzylamino-1-aza-1-cycloheptene *(9)* and 2-butylamino-1-aza-1-cycloheptene *(10)* can be used as model substances for the investigation of semicyclic amidine groups in thermally damaged nylon 6[129].



(9), R = CH_2-C_6H_5
(10), R = n-C_4H_9

Dinitrophenylation experiments on these compounds[*] show that both the exocyclic and the endocyclic amidine nitrogen react with DNFB, but that the reaction does not proceed uniformly[129a].

A comparison of the spectrum of peramidinated and dinitrophenylated nylon 6 with that of a thermolyzed product (30 h at 185—195 °C in the absence of oxygen) that had subsequently been deaminated[130] and then dinitrophenylated shows good agreement (Fig. 9, curves b and c respectively). As when dinitrophenylated secondary amino groups are present, a change in the extinction ratio E^{350}/E^{390} is found in relation to untreated nylon 6 containing only primary amino groups (Fig. 9, curve a).

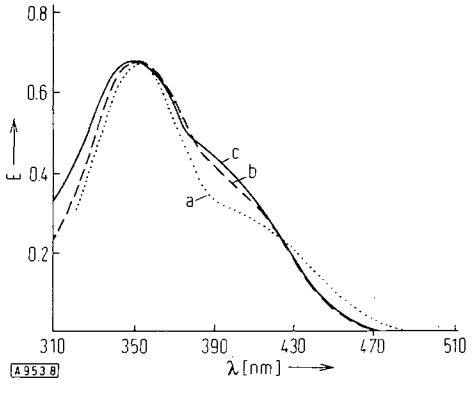


Fig. 9. Spectra of a) dinitrophenylated nylon 6 (c = 0.065 %), b) peramidinated and dinitrophenylated nylon 6 (c = 0.60 %) and c) thermolyzed, deaminated, and dinitrophenylated nylon 6 (c = 1.1 %) in 2,2,2-trifluoroethanol.

[*] Reference substances were kindly supplied by Prof. Dr. *H. Herlinger*, Stuttgart.

This may be taken as the first direct evidence that the non-deaminatable basic groups formed in nylon 6 by the action of heat are amidine groupings. The spectra of nylon 6,6 samples treated in the same way indicate that amidines are also formed here by thermolysis. Attempts by *Schlack* and *Rieker*[131] to prove the existence of these groups in peramidinated polycaprolactam by removal and isolation of the amidine heterocycle were successful only for low molecular weight model substances. On the other hand, they have been detected by thin layer chromatography[132] and determined indirectly by titration[133] in cationically polymerized nylon 6.

4.3. Determination of the Hydroxyl End Groups of Polyesters

For a chemical determination of the hydroxyl end groups, these groups must first be allowed to react with a reactive compound. Because of the low content of these groups in fiber-forming polyesters[145], calculation by measurement of the excess reagent after the manner of a back-titration, as suggested by a number of authors[134–140], seems problematic[141]. Direct methods are based on the determination of the groups introduced into the polymer in polymer-analogous reactions (carboxyl[142], haloacyl[143–148], *N*-phenylcarbamoyl[136, 149, 150], benzoyl[151], sulfosalicyl groups[152]). However, analyses of this nature require an additional determination of the original carboxyl group content (this also applies to the repeatedly described determinations by exchange of active hydrogen atoms with isotopes[153]) or a multiple quantitative reaction of the polymer.

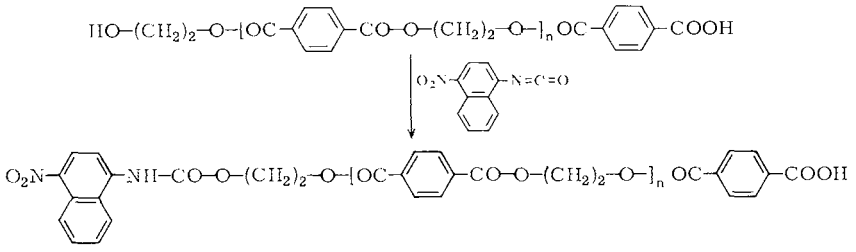
The reaction with phenyl isocyanate was first used by *Griehl* and *Neue* for the determination of hydroxyl groups in PET[143]. These authors, and also *Batzer* and *Mangold*[154] and *Gaylord* and *Rosenbaum*[155], who allowed PET to react with hexamethylene diisocyanate, determined the hydroxyl group content from a nitrogen analysis of the polyester urethane obtained; because of the very low nitrogen contents, however, this cannot yield satisfactory results. The accuracy of the phenyl isocyanate method was improved by the work of *Kern*[149] and of *Hendrix*[56], but the analytical procedure required is complicated. The polyester urethane formed is hydrolyzed to remove aniline, which is diazotized, coupled with 1-naphthylethylenediamine or 2-naphthol, and determined colorimetrically.

The use of a colored isocyanate, on the other hand, decisively simplifies the determination of the hydroxyl end groups[133].

4.3.1. Principles of the Determination of Hydroxyl End Groups with 4-Nitro-1-naphthyl Isocyanate

The reaction of PET with 4-nitro-1-naphthyl isocyanate (NNI) yields a yellow *N*-(4-nitro-1-naphthyl) urethane of the polymer, whose chromophore absorbs independently of the structure of the rest of the molecule, as has been

shown for *N*-(4-nitro-1-naphthyl) urethanes of ethylene terephthalate oligomers (Fig. 10).



The polyester material is dissolved in nitrobenzene, and sufficient NNI in nitrobenzene is added to make the solution 1% with respect to polyester and 1.8% with respect to NNI. After five hours at 130 °C, the *N*-(4-nitro-1-naphthyl) urethane of the polyester is precipitated in ten times as much ether, reprecipitated twice from nitrobenzene with ether, and finally extracted with ether. The polyester urethane is dissolved in phenol/*o*-dichlorobenzene (3:2) and determined photometrically at 375 nm. The content of hydroxyl groups is calculated with the aid of a calibration curve plotted for *N*-(4-nitro-1-naphthyl) urethanes of the

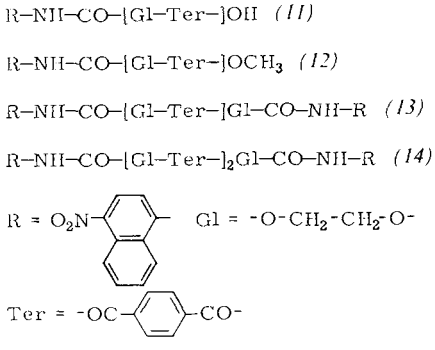


Fig. 10. Calibration line for the determination of the hydroxyl end group concentration from the molar extinction (at 375 nm) of PET treated with 4-nitro-1-naphthyl isocyanate (NNI). The calibration line was plotted for the *N*-(4-nitro-1-naphthyl) urethanes *(11)*–*(14)* of ethylene terephthalate oligomers.

ethylene terephthalate series. The hydroxyl end groups are thus determined by a single chemical reaction of the polymer. This leads to only small quantities of by-products of the reagent, which can be removed without difficulty by reprecipitation. As investigations on oligomers have shown, reaction of carboxyl groups of the polyester with the isocyanate takes place to a negligible extent, if at all, under the conditions used[156].

Table 8 shows a comparison of the results of the NNI method with those of the method described by *Conix*[142], which requires a double determination of the carboxyl group content before and after the reaction of the hydroxyl groups with succinic anhydride and has a large confidence belt[139].

Table 8. Determination of the hydroxyl end groups of commercial PET fibers by reaction with succinic anhydride [142] and with 4-nitro-1-naphthyl isocyanate (NNI).

Producer, trade name, degree of delustering [a]	OH [meq/kg] with succinic anhydride [b]	with NNI [c]
Hoechst Trevira 220, mt	55	54
Enka Diolen FL, gl	66	60
ICI Terylene W16, hm	73	79
Rhodiaceta Tergal, mt	51	57

[a] gl = bright, hm = semi-dull, mt = dull.
[b] Initial content of carboxyl groups: see Table 3.
[c] Coefficient of variation = 2.4%; confidence belt = ±2.2 meq/kg (for 95% statistical certainty).

4.3.2. Application of the Hydroxyl End Group Determination with 4-Nitro-1-naphthyl Isocyanate

The hydroxyl group contents found by the NNI method for PET homopolyesters are between 35 and 79 meq/kg, depending on the manufacturer and the intended use (Table 9).

These values together with the results obtained by the hydrazinolysis method give remarkable differences in the ratios of hydroxyl to carboxyl groups in the fibers investigated; this ratio can play an important part in the thermal behavior of the polyester[44,45]. The molecular weights $\overline{M}_n$ (number average) were calculated from the results given by the determination methods developed for both end groups, the methyl ester end groups that may be present in very small concentrations in PET[157] being disregarded. As was shown by *Zimmermann* and *Becker*[43], however, a complete end group analysis should include testing for methyl ester groups, since these can interfere with the polycondensation, and their content in the PET should yield information on the course of the production process.

The molecular weights obtained for the PET homopolyester fibers of the normal type are between 23000 and 28000, and correspond to data in recent publications[40,45,66,158]. Low molecular weights (approx. 17000) were found for the two pilling-resistant PET fiber types; the low molecular weights are probably responsible for this property of the fibers[40,66,159].

Table 9. End group content and molecular weight ($\overline{M}_n$) of commercial PET fibers.

Producer, trade name, degree of delustering [a]	[η] [156] [dl/g]	COOH [meq/kg] Hydrazinolysis	OH [meq/kg] NNI method	[OH]/[COOH]	$\overline{M}_n$
Hoechst Trevira 220, mt	0.47	22	54	2.5	26300
Hoechst Trevira 220, gl	0.44	20	52	2.6	27800
Enka Diolen, gl	0.47	40	35	0.9	26700
Enka Diolen FL, gl	0.38	59	60	1.0	16800
ICI Terylene W11, gl	0.44	32	44	1.4	26300
ICI Terylene W16, hm	0.37	37	79	2.1	17200
Rhodiaceta Tergal, mt	0.47	26	57	2.2	24100
Rhodiaceta Tergal, hm	0.45	25	63	2.5	22700

[a] gl = bright, hm = semi-dull, mt = dull.

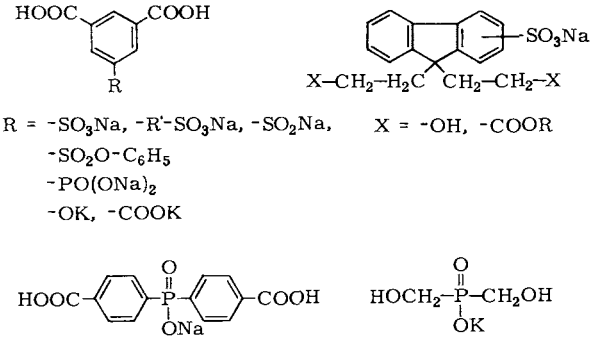
5. Determination of Comonomers in Polyesters and Polyacrylonitrile

5.1. Investigation of Chemically Modified Polyesters

The difficulty of dyeing of polyester fibers and their susceptibility to pilling can be problematic in practice. In efforts to overcome these difficulties, the homopolyester of terephthalic acid and ethylene glycol has been subjected to numerous chemical modifications by copolymerization of a third component[40,66]. In this way, the dyeability with dispersed dyes can be improved (Table 10) or dyeing with basic dyes can become possible (Fig. 11). On the other hand, no technically and economically satisfactory solution has so far been found to the problem of the modification of PET for dyeing with anionic dyes, owing to the thermal sensitivity of the required modifying components containing basic nitrogen.

There have been only a few publications dealing with the quantitative determination of comonomers in chemically modified polyesters. These are concerned with the examination of the total hydrolysis product of the polymer and the use of spectroscopic detection methods (IR, NMR)[160].

1) incorporation of co-components during polymer production



2) incorporation of anionically active substances prior to or during the spinning process

3) after-treatment of filaments and fibers with SO_3, SO_2Cl_2, and $ClSO_3H$

Fig. 11. Modification of PET to allow dyeing with cationic dyes [66].

Table 10. Modifying components for PET to improve the affinity for disperse dyes [66].

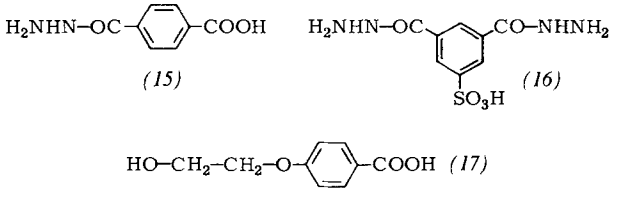
Dicarboxylic acids	Hydroxy carboxylic acids	Diols and monofunctional polyalkylene oxides
HOOC–(CH2)n–COOH n = 3, 4, 6, 7, 8, 10	HO–(CH2)5–COOH	HO–(CH2)n–OH n = 3, 4, 5
HOOC, COOH	CH3 HOCH2–C–COOH CH3	CH3 HOCH2–C–CH2OH CH3
HOOC–COOH	HO–COOH	HOH2C, CH2OH
HOOC, COOH [a]	HO–(CH2)n–O–COOH n = 2, 3	HO–(CH2)2–O–(CH2)2–OH
HOOC–CH2–CH2–COOH		CH3 H(O–CH2–CH2)n–O–C–O–(CH2–CH2–O)nH CH3 n = 0, 1
HOOC–CO–COOH		HO–(CH2–CH2–O)nH n ≈ 10...150
HOOC–(CH2)3–SO2–(CH2)3–COOH		RO–(CH2–CH2–O)nH n ≈ 10...150

[a] Substitution products are also suitable.

5.1.1. Determination of Aromatic Comonomers with Acidic Substituents

The hydrazinolysis method is also suitable for the investigation of chemically modified polyesters, and in addition to the determination of carboxyl end groups it also allows the quantitative determination of aromatic comonomers with acidic substituents[133]. Thus on ion exchange of the hydrazinolysis products of basically dyeable polyester fibers copolymerized with sodium 5-sulfoisophthalate, the hydrazides of the comonomer are isolated because of their unchanged sulfo group, as well as terephthalomonohydrazide.

The ion-exchange eluate may be regarded as a two-component system if no differentiation is made between the sulfoisophthalic acid derivatives (dihydrazide and monohydrazide) that are isolated together with terephthalomonohydrazide. A quantitative simultaneous determination of the comonomer content and of the carboxyl end groups, which are equivalent to the C-terminal terephthalic acid, thus becomes possible. Terephthalomonohydrazide *(15)* and 5-sulfoisophthalodihydrazide *(16)* are used as calibration substances for the development of a two-component analysis based on the difference in the spectral behavior of the compounds (Fig. 12).



$c_1 = (6.21 \times E^{240} - 1.04 \times E^{212}) \times 10^{-5}$ mol/l

$c_2 = (2.62 \times E^{212} - 0.51 \times E^{240}) \times 10^{-5}$ mol/l

c_1, c_2 = concentration of terephthalomonohydrazide and 5-sulfoisophthalodihydrazide respectively

E^{240}, E^{212} = extinctions at 240 and 212 nm

For three basically dyeable PET copolyester fibers, comonomer contents of 1.6 to 1.8 mol % of sodium 5-sulfoisophthalate were found, based on the monomer unit [$OCH_2CH_2OOC—C_6H_4—CO$] (Table 11). These results are lower than the values given in the literature[160, 161].

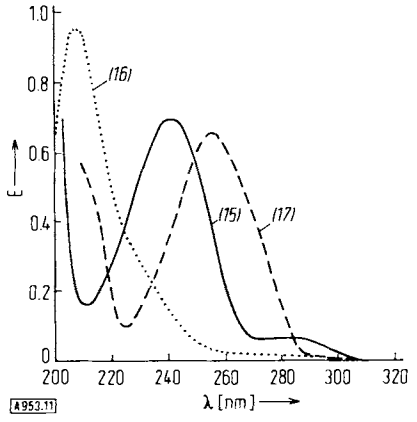
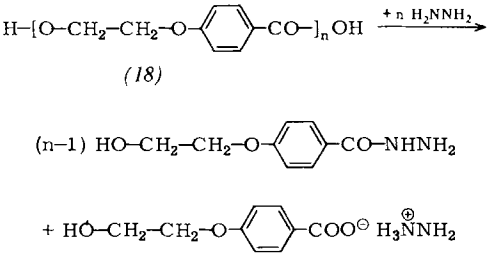


Fig. 12. UV spectra (in 0.1 N HCl) of terephthalomonohydrazide *(15)*, *p*-(β-hydroxyethoxy)benzoic acid *(17)* ($c = 4 \times 10^{-5}$ mol/l), and 5-sulfoisophthalodihydrazide *(16)* ($c = 2 \times 10^{-5}$ mol/l).

5.1.2. Determination of Aromatic Hydroxy Carboxylic Acids

The ester linkages in homo- and copolyether ester fibers with *p*-(β-hydroxyethoxy)benzoic acid *(17)* as the monomer unit or comonomer unit are also quantitatively broken by hydrazine, though only after a longer reaction time.



In the case of poly-[*p*-(2-ethylenoxy)]benzoate (A-Tell) *(18)*, the hydrazinolysis method results in the isolation of *p*-(β-hydroxyethoxy)benzoic acid *(17)*, which is equivalent to the C-terminal carboxyl groups of the polymer, and which is quantitatively determined with the corresponding pure compound as the calibration substance (Table 11).

The hydrazinolysis products of the copolyether ester, on the other hand, yield terephthalomonohydrazide *(15)* and *p*-(β-hydroxyethoxy)benzoic acid *(17)*, which correspond to different C-terminal monomer units. The ratio of the numbers of monomer units carrying carboxyl groups

Table 11. Contents of carboxyl end groups and of comonomers in copolyester and homopolyether ester fibers.

Producer, trade name	C-terminal terephthalic acid [mmol/kg]	C-terminal *p*-(β-hydroxyethoxy)benzoic acid [mmol/kg]	5-Sulfoisophthalic acid [mmol/kg]
DuPont Dacron 64c	21	—	86
DuPont Dacron 65	35	—	94
DuPont Dacron 89	38	—	82
Unitika Copolyether ester	29	8	—
Unitika A-Tell (homopolyether ester)	—	32	—

can be determined by a photometric two-component analysis developed with the pure compounds. This may be regarded as the first step toward a chemical sequence analysis of this polymer, which has so far been attempted only with the aid of high-resolution NMR spectroscopy[160].

$c_1 = (7.65 \times E^{240} - 3.27 \times E^{258}) \times 10^{-5}$ mol/l

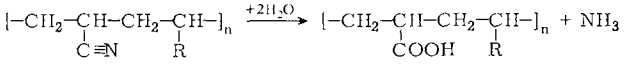
$c_2 = (7.91 \times E^{258} - 3.49 \times E^{240}) \times 10^{-5}$ mol/l

c_1, c_2 = concentration of terephthalomonohydrazide and *p*-(β-hydroxyethoxy)benzoic acid

E^{240}, E^{258} = extinctions at 240 and 258 nm

5.2. Investigation of Copolymerized Polyacrylonitrile

The comonomers present in commercial polyacrylonitrile fibers (Fig. 4) can be determined directly, according to *Hilden*, by hydrolysis of the nitrile groups[88], with quantitative formation of carboxyl groups and ammonia; the ammonia can be easily determined by titration, and the content of nitrile groups can be calculated from the result.



However, no differentiation is possible in this method between hydrolyzable nitrile groups and amide groups. The content of incorporated comonomer is deduced from the difference between the nitrile content expected for pure acrylonitrile and that found for the polymer in question. The comonomer contents obtained in this way vary widely from one fiber to another (6 to 14%, Table 12).

6. Determination of Extraneous Substances

Dyeability and strength, as the most important textile properties, are determined by the chemical structure and fine structure of the polymers. The extraneous substances, however, must also be taken into account in the analysis of synthetic fibers. These include preparing agents, delustering agents, optical brighteners, light stabilizers, heat stabilizers, antistatics, *etc.*, which are added to the fiber polymers to modify their application properties.

Since the substances mentioned belong to very different classes, which may be present *e.g.* even in a single spinning oil, it seems impossible to find any generally applicable methods. Since the treatment of synthetic fibers with these additives is undergoing constant development and modification, it is extremely difficult to analyze them qualitatively and quantitatively[162-165].

However, the importance of these investigations is shown *e.g.* by the influence of surface-active compounds, *e.g.* in spinning oils, on the viscosity behavior[166], on titrimetric end group determinations[32,33], and on the dyefastness of the fibers[167]. Methods for the analysis of wool[168] appear to be of only limited value for the determination of extractable ionic substances[32,33].

A spectrophotometric determination of phosphorus, which is important in connection with stabilizers containing phosphorus[52], has been described by *Telep* and *Ehrlich*[169]. *Dinse* and *Ewert*[170] have developed a polarographic method for the determination of titanium dioxide in PET and nylon 6 materials. Polarography[171], atomic absorption spectroscopy[172], X-ray fluorescence spectroscopy, and neutron activation analysis[32,33,158] are suitable for the determination of titanium and for the analysis of traces of heavy metals, which may come from impurities, catalyst residues, or labeling additives. The determination of the heavy metal content shows very clearly the importance of the analysis of extraneous substances, since heavy metals can influence the stability of the fibers to light, heat, and thermal oxidation.

Table 12. Contents of acrylonitrile and of comonomers in commercial polyacrylonitrile fibers [88].

Producer, trade name	Experimental acrylonitrile content [%]	Calculated comonomer content [%] from nitrile group content	from nitrogen content
Bayer Dralon	90.5	9.5	9.6
Bayer Dralon bifilar	89.9	10.1	9.9
DuPont Orlon 42	90.4	9.6	9.5
DuPont Orlon 74	86.0	14.0	9.6
DuPont Orlon 75	91.2	8.8	8.9
DuPont Orlon 75B	94.1	5.9	9.8
Phrix Redon F	91.0	9.0	8.9
Hoechst Dolan 50	91.5	8.5	7.2

As a comparison, the comonomer content was also determined from the content of nitrile groups, which can be calculated from the result of a Kjeldahl nitrogen determination. In the case of Orlon 74, a considerably higher comonomer content is found by hydrolysis than by elemental analysis; this means that part of the nitrogen contained in this fiber is present in an unhydrolyzable form. This fact, the characteristic IR spectrum, and the dyeability with acid dyes[88] support the assumption that this fiber contains a heterocyclic amine (*e.g.* vinylpyridine), a conclusion that cannot be drawn from the nitrogen analysis alone.

7. Conclusion

In the foregoing discussions, we have described new specific chemical methods for the determination of functional

groups in polymers, which allow more far-reaching conclusions to be drawn regarding the chemical structure and the behavior of synthetic fibers than *e.g.* from most of the titration methods used. Methods were shown for the recognition of fiber damage and the quantitative chemical determination of comonomers. It is clear that the chemistry of natural macromolecular products, which has already provided the stimulus for the synthesis of fiber-forming polymers, is also a fruitful basis for their analysis.

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Chemistry and Applications of Liquid Crystals

By Ralf Steinsträsser and Ludwig Pohl[*]

Approximately 5% of all organic compounds are transformed at their melting point into liquid crystals—thermodynamically stable, anisotropic liquids which in contrast to isotropic melts appear turbid and are also known as mesophases. Such melts are classed as smectic, nematic, and cholesteric liquid crystalline phases, depending upon the arrangement of the constituent molecules. The discovery of numerous potential applications during the past ten years has awakened the study of liquid crystals from its former slumber as a physical curiosity and placed it in the limelight of the scientific stage. Uses in display systems for measured values and for computer and process data, as well as for remote controlled timetables, for windows of variable light-transmission, *etc.*, appear particularly promising. Not only black-and-white contrasts are now possible but also color production.

1. Introduction

Directionally dependent (anisotropic) properties are observed independently of the state of aggregation only for substances having a regular arrangement of constituent molecules. If the order is three-dimensional in nature then the substance is a crystalline solid, while two- or one-dimensional order is characteristic of crystalline liquids or liquid crystals[1-5].

The main emphasis of the present progress report will be placed on recent applications of liquid crystals and on the connection between chemical structure and the principal physical effects.

2. Structure and Properties of Liquid-Crystalline Phases

Smectic, nematic, and cholesteric liquid-crystalline phases can readily be distinguished on the basis of their optical, rheological, and thermodynamic properties. The structures characteristic of smectic phases were first observed with soaps (Greek σμῆγμα) under the polarizing microscope. The nematic phases owe their name to their threadlike (Greek νέματος) appearance under the polarizing microscope. And finally the designation cholesteric derives from cholesterol whose derivatives were the first compounds seen to exhibit such phases.

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2.1. Smectic Liquid-Crystalline Phases

Smectic phases have a two-dimensional structure. As seen in Figure 1 their molecules are arranged in layers. Since hardly any interaction occurs between the ends of the molecules the layers can readily slip over one another. The high viscosity and surface tension of smectic phases are a consequence of the high degree of order.

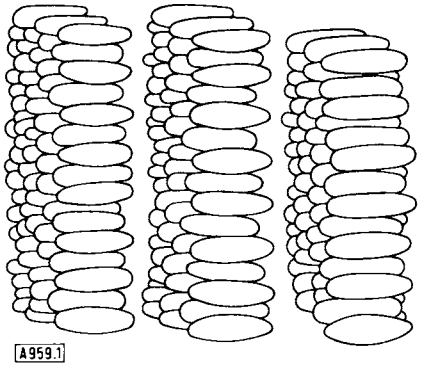
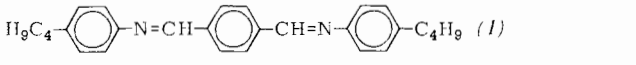


Fig. 1. Structural model of a smectic phase.

Depending on the molecular arrangement it is possible to distinguish at least five different smectic states which are classified by the symbols A to E according to *H. Sackmann* and *Demus*[2]. Three additional smectic phases designated F, G[6], and H[7] have also been proposed. Pure compounds too, on warming or cooling, can pass through several smectic phases bounded by first-order

transition points. The transition points of such polymorphous systems can be determined by differential thermal analysis (DTA). Figure 2 shows the DTA curves of *p*-bis(*p*-*n*-butylphenyliminomethyl)benzene *(1)*, a compound for which *Taylor et al.*[8] observed one nematic and three smectic phases (S_A, S_C, S_B). The upper curve a) was recorded on warming of the crystalline solid and the lower one b) on cooling of the isotropic melt. Phase transitions between several liquid crystalline phases and the isotropic phase cannot be supercooled.



(1)

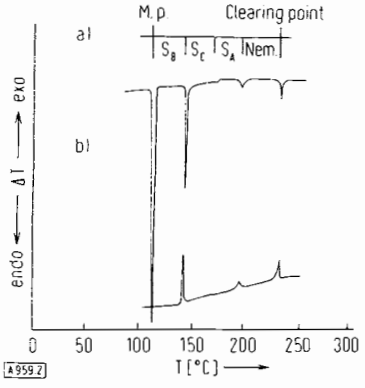


Fig. 2. Differential thermal analysis of *p*-bis(*p*-*n*-butylphenyliminomethyl)-benzene *(1)*; a) heating curve, b) cooling curve.

The identification and assignment of smectic phases has been pursued in recent years above all by *H. Sackmann et al.*[2,9–12]. Apart from thermal analysis, three main methods of study are preferred.

2.1.1. Microscopic Studies

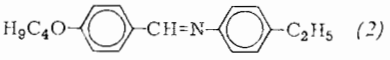
In most cases characteristic patterns can be recognized under the microscope when liquid crystalline preparations are viewed between crossed Nicols. These textures arise from the differing orientation of the optical axes of adjacent regions that are in themselves optically homogeneous. The boundary lines between these regions, the lines of discontinuity, are typical of the textures which permit a first, albeit not always unequivocal, distinction of the various smectic phases. The three smectic phases characterized thermoanalytically in Figure 2 were found to give a focal conic (S_A), a smectic schlieren (S_C), and a mosaic texture (S_B)[8].

2.1.2. Miscibility Relationships in Binary Systems[2,10–12]

Evaluation of phase diagrams of two compounds having liquid-crystalline properties assumes that perfect miscibility of two anisotropic phases is only possible if both have the same kind of structure. Perfect miscibility of an unknown smectic phase with a component known to be, *e.g.* S_B, would indicate the presence of a smectic B phase. This method has been employed to establish the identity of numerous phases formerly known merely as "smectic".

2.1.3. X-Ray Analysis[7,13–16]

The layer arrangement of the molecules could be confirmed for the A, B, and C phases by X-ray diffraction diagrams[15]. Such an arrangement, although of higher order, is highly probable also for the smectic E phase, while a cubic structure is under discussion for the smectic D phase.



(2)

The smectic H modification was found by *de Vries et al.*[7] for *p*-ethyl-*N*-(*p*-*n*-butoxybenzylidene)aniline *(2)* between 40.4 and 51 °C and classified on the basis of X-ray diffraction and microscopic investigations. A three-dimensional layer structure has been proposed in which the long molecular axes are inclined to the plane of the layer and the molecular planes adopt a herringbone arrangement.

This example clearly demonstrates that it is often difficult to distinguish between a solid and a liquid crystalline state. While the high order suggests a second solid crystalline modification, the fact that the phase transition at 51 °C cannot be supercooled indicates the existence of a true liquid crystalline phase which shows the known smectic textures under the polarizing microscope. The lines of discontinuity merge and reorder themselves when a shearing force is exerted on the objects by application of light pressure with a needle or by lateral displacement of the cover glass[7].

The only significant application of smectic phases discovered so far is their use as solvents in ESR and Mössbauer spectroscopy (cf. Sections 5.3 and 5.4)[*].

2.2. Nematic Liquid-Crystalline Phases

The uniform order within a molecular plane of smectic systems is absent from nematic phases (Fig. 3). The latter merely exhibit a time- and spatially averaged parallel orientation of the long molecular axes within relatively small regions and are consequently much less viscous than smectic phases[17].

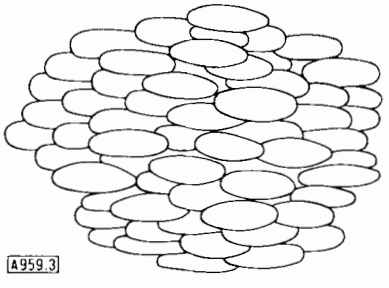


Fig. 3. Structural model of a nematic phase.

The ideal case—*i.e.* parallel orientation of all molecules over large regions—can only be achieved by expenditure

[*] *Note added in proof* (July 23, 1973): It has meanwhile been found that smectic C phases are suited for the production of electrooptical memory devices [188].

of additional energy, *e.g.* by electric or magnetic fields. In real nematic liquids, however, the preferred orientation is subject to continuous change, the angle by which the preferred direction changes from place to place not being defined as it is in cholesteric liquid crystals (Section 2.3).

The quality of the parallel orientation can be characterized by the degree of order S which is unity for the ideal nematic phase and zero for the isotropic phase. It has a value between 0.3 and 0.8 for normal nematic liquid crystals and decreases steadily with rising temperatures, suddenly falling to 0 at the transition point to the isotropic melt[13, 18].

Nematic "single crystals" ($S=1$) are optically and dielectrically uniaxial, the symmetry axis running parallel to the molecular axis. The values of the dielectric constant ε, the susceptibility χ, the refractive index n, or of other anisotropic properties measured in this direction are given the subscript 1, and the values measured in a perpendicular direction the subscript 2. In nematic liquid crystals the molecular long axis is also the direction of maximum polarizability of the molecule; thus a positive birefringence ($n_1 > n_2$) is always observed[19–22].

The diamagnetic anisotropy of nematic phases ($\Delta\chi = \chi_1 - \chi_2$) is also always positive since the susceptibility is always greater along the molecular long axis than in the perpendicular direction.

In contrast, the dielectric anisotropy ($\Delta\varepsilon = \varepsilon_1 - \varepsilon_2$) can be positive or negative and depends upon the varying contributions of shift and orientation polarization in the different axial directions which are determined by the molecular structure[23, 24].

Uniformly oriented nematic preparations also exhibit anisotropic electric conductivity[25–29], thermal conductivity[30, 31], ultrasonic velocity[32], diffusion[33], and viscosity[34]. Values of anisotropic measurements must always be accompanied by the measuring temperature since they are all strongly temperature-dependent. The manifold applications of nematic phases will be described in Section 4.

2.3. Cholesteric Liquid-Crystalline Phases[1, 3]

The cholesteric mesophase represents a special case of the nematic structure in that it is also characterized by a parallel orientation of the long axes of the molecules which however varies regularly from place to place. As shown in Figure 4 there is a uniform preferred direction within a given layer which is rotated in a uniform direction through a constant angle relative to that in the adjacent layer. Seen over several layers this leads to a skewed arrangement of the molecular layers[35]. The twisted structure and the sense of the rotation are induced by the chiral form of the participating molecules. Cholesteric phases were first observed in cholesterol derivatives.

Mixing of cholesteryl esters having right-handed and left-handed helical arrangements in a particular ratio and at a definite temperature, the nematic temperature T_n, at which the rotatory powers of the components cancel each other, leads to a nematic liquid crystal which is termed a compensated cholesteric liquid crystal[36]. Such cholesteric-nematic phase transitions can be induced not only thermally but also by application of electric[37, 38] and

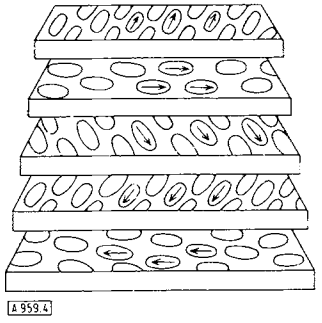


Fig. 4. Structural model of a cholesteric phase. The preferred orientation of the long molecular axes within a layer is rotated through a constant angle relative to that within the adjacent layer (helical structure).

magnetic fields[39, 40]. Moreover, the cholesteric structure can also be produced by addition of a chiral, not necessarily liquid-crystalline, compound to a nematic liquid[41] or by resolution of nematic racemates[42], thus clearly illustrating the close relationship between cholesteric and nematic structure.

Most of the optical properties result from the twisted structure, *e.g.* the extremely high optical rotation, the circular dichroism, and the technically important selective reflection of the spectral region whose wavelength corresponds to the pitch of the helix[43]. A change in pitch caused by thermal[43, 44], magnetic[45], or electrical energy[46–48] manifests itself in a change in optical properties.

Of particular importance in practice is the temperature dependence of selective reflection in the visible spectrum because it enables cholesteric liquid crystals to be used as temperature indicators in medical diagnoses[49, 50], in nondestructive testing of materials[51, 52], or for infrared image converters[53]. Experiments have also be performed to exploit this effect for the production of color TV tubes[54, 55] but have so far been thwarted by the difficulties inherent in converting an electrical impulse into a local warming effect in a manner satisfying practical requirements. Other electrooptical applications of cholesteric liquid crystals are based either on the above mentioned cholesteric-nematic phase transition by electric fields[46] or on the conversion of the transparent planar cholesteric texture into the strongly dispersive focal conic texture, which opens up the possibility of producing optical storage systems[56–58] (cf. Section 4.4).

3. Relationship between Chemical Structure and the Occurrence of Liquid-Crystalline Phases

Recent studies on the relationship between molecular structure and the appearance of anisotropic mesophases have been performed mainly by *Brown*[59], *Dave*[60], *Gray*[1, 61], *de Jeu*[62], *Kast*[63], and *Wiegand*[64]. *Kast* also compiled a list of all compounds known up to 1959 that possess liquid-crystalline properties[65].

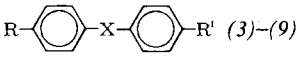
3.1. Molecular Structure of Nematic and Smectic Compounds

The thermodynamic stability of liquid crystalline phases can be characterized in terms of the clearing point, *i.e.* the temperature at which the energy content of the anisotropic and the isotropic liquid is equal and both modifications are present.

Comparison of the clearing points of compounds of analogous structure differing only in one particular feature permits assignment of the contribution of such partial structures to liquid-crystalline character. The most important knowledge gained in this way will now be summarized and illustrated with the aid of a characteristic example:

The greater the anisotropy of the polarizability of a molecule, the higher the clearing point and the stability of mesophases. Accordingly, the compounds forming liquid crystals generally are composed of long, planar rigid molecules usually consisting of a conjugated aromatic system.

Table 1. Compounds of types *(3)*—*(9)*.



(3)–*(9)*

Type	X	Name	Ref.
(3)	—CH=CH—	*trans*-stilbenes	[66]
(4)	—C≡C—	tolanes	[67]
(5)	—N=N—	azobenzenes	[68, 69]
(6)	—N=N— (O)	azoxybenzenes	[70, 71]
(7)	—CH=N(O)—	nitrones	[72]
(8)	—CH=N—	Schiff bases	[73, 74]
(9)	—O—CO—	phenyl benzoates	[75]

Compounds of types *(3)* to *(9)* (Table 1) have been intensively studied[76–78] in connection with the applications considered in Section 4. Of the stilbenes *(3)*, only the *trans* isomers are able to form liquid-crystalline phases. Although the correspondingly substituted *cis*-stilbenes are also planar they do not have a linear molecular structure. Owing to their low degree of conjugation the esters *(9)* have the lowest clearing points. Methyl substituents *ortho* to the bridge or on the bridge itself in the case of stilbene effect mutual twisting of the phenyl rings for steric reasons, thus reducing the polarizability along the long molecular axis and thereby the stability of the mesophase[66, 79]. Replacement of aromatic rings by bi- or mono-cyclic aliphatic systems has a similar effect[80, 81]. Additional permanent dipoles shift the clearing points to higher temperatures. Whereas the central bridge of the molecule induces anisotropic melting properties, the nature and chain length of the wing groups determine which of the mesophases occurs.

If the wing groups are ether or ester groups linked to the molecular skeleton *via* oxygen, the lone pairs also contribute to the π-electron system, thus enhancing the thermal stability of the mesophases:

(6a), R = R′ = *n*-C_4H_9 [69], clearing pt. 28 °C (m. p. 14 °C)
(6b), R = *n*-C_4H_9, R′ = OC_4H_9 [70], clearing pt. 91 °C (m. p. 37 °C)
(6c), R = R′ = OC_4H_9 [82], clearing pt. 137 °C (m. p. 102 °C)

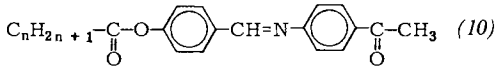
Table 2 illustrates the effect of varying the wing groups on the liquid-crystalline properties of a homologous series[83].

The acetic ester *(10)*, $n=1$, goes directly from the solid to the isotropic liquid state at 114.5 °C; only on careful supercooling to 105 °C does the latter phase yield a metastable nematic phase. Such systems are termed monotropic. An enantiotropic, *i.e.* thermodynamically stable, nematic phase is observed for the propionic ester *(10)*, $n=2$. The compounds with $n=3$ and 4 also give monotropic smectic phases in addition to enantiotropic nematic phases, while both the nematic and the smectic phases of the higher homologs ($n=5$—7) are enantiotropic.

As the chain length increases, the tendency to form smectic phases increases at the expense of the nematic phase until eventually only smectic phases are observed at a chain length of, in the present case, more than seven carbon atoms.

This behavior has been observed in all homologous series of ethers, esters, ketones, or directly linked alkyl chains in various classes of compounds and can therefore be generalized.

Table 2. Transition points [°C] of a homologous series of type *(10)* [83]. Monotropic transitions are indicated in parentheses.



(10)

n	solid/ isotropic	smectic [a]		nematic	anisotropic/ isotropic (clearing pt.)
1	114.5	—			(105.0)
2		—		106.0	113.0
3		S_A:	(73.5)	87.5	115.0
4		S_A:	(84.0)	101.0	105.5
5		S_C:	86.5	92.0	110.5
6		S_C:	94.5	100.0	107.0
7		S_C:	89.0	107.0	111.5
8		S_C:	83.0	—	111.5
9		S_C:	79.0	—	116.0

[a] S_A and S_C signify smectic A and C phases. Further transitions to monotropic smectic phases were observed.

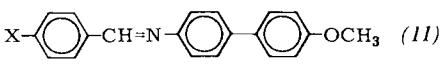
Table 2 also reveals another generally valid principle: the clearing points alternate within a homologous series, usually diverging towards lower values but sometimes also to higher values[62].

Chain branching in the substituent reduces the tendency to form anisotropic melts because steric hindrance precludes an optimum parallel arrangement of the molecular skeletons. The intramolecular steric hindrance increases the nearer the branching point approaches the rigid central part of the molecule[84].

Young et al.[85] found that incorporation of a particularly readily polarizable atom can compensate the unfavorable steric effect of chain branching. While the *tert*-butyl com-

pound *(11a)* is not liquid crystalline, the trimethylsilyl *(11b)*, trimethylgermyl *(11c)*, and trimethyltin *(11d)* analogs form smectic mesophases (Table 3).

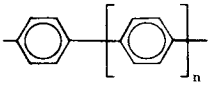
Table 3. Melting and clearing points [°C] of compounds *(11a)*—*(11d)*.



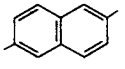
(11)

Cpd.	X	m.p.	clearing point
(11a)	$(CH_3)_3C$	190	—
(11b)	$(CH_3)_3Si$	180	183
(11c)	$(CH_3)_3Ge$	176	175 (monotropic)
(11d)	$(CH_3)_3Sn$	165	173

The central part of the molecule can be modified in a variety of ways. Thus when bearing suitable substituents, compounds having the structural features *(12)*—*(18)* exhibit liquid crystalline behavior[1,165] [X and Y in *(15)* have the same significance as in compound *(1)* and the compounds of types *(3)*—*(9)*]. Free carboxylic acids, such as *para*-substituted benzoic or cinnamic acids, occur as double molecules in the melt and thus form a planar system of sufficient length.



(12) [86, 87]



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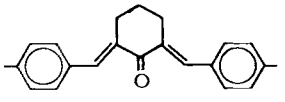

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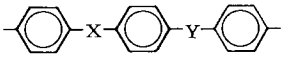

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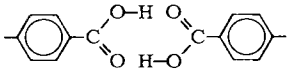

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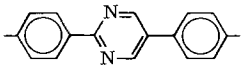
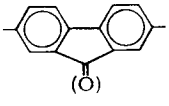


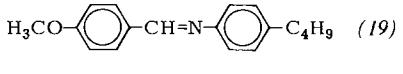
(17) [88]



(18)

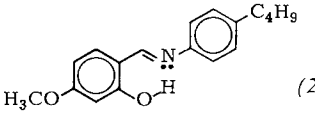
3.2. Nematic Liquid Crystals Having Special Properties

Subsequent to the discovery of their possible electrooptical applications (Section 4) an intense search was instituted for suitable nematic substances having low melting points and high clearing points, favorable anisotropic properties, and adequate stability towards chemical and physical effects.



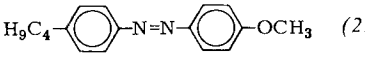
(19)

The first nematic compound found to be a liquid at room temperature, *p-n*-butyl-*N*-(*p*-methoxybenzylidene)aniline (MBBA) *(19)*, m.p. 20 °C, clearing point 47 °C, was described in 1969 by *Kelker et al.*[73]. Moreover, binary eutectic mixtures of Schiff bases have been prepared, some of which melt far below 0 °C[73,74]. However, since the sensitivity of Schiff bases to hydrolysis severely impairs their technical utilization, attempts are made to stabilize them by introduction of an intramolecular hydrogen bond as in compound *(20)*, m.p. 44.7 °C, clearing point 64.5 °C[89]. A significant but insufficient stabilization is noted. The increase in the clearing point is accompanied by an increase in melting point compared to compound *(19)*.



(20)

Studies on more stable structural types showed that the substituent combination *p-n*-butyl/*p*-methoxy also leads to the lowest melting representatives *(21)* and *(22)*, respectively, of the azo- and azoxybenzenes[68,70] [*(21)*, m.p. 32 °C, clearing point 47 °C; *(22)*, m.p. 16 °C, clearing point 76 °C]. The azoxy product *(22)* consists of a mixture of the two N—O isomers. Admixture of 35% of the isomeric pair *p*-ethyl-*p*-methoxyazoxybenzene gave a eutectic (clearing point 75 °C) melting at −5 °C[70].



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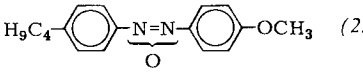
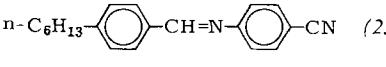


(22)

The azomethines and azoxybenzene derivatives mentioned so far exhibit a negative dielectric anisotropy. If there is no permanent electric dipole perpendicular to the long molecular axis (ε_2) or the *para* position carries a strongly polar group, then the dielectric constant ε_1 in the direction of the long axis will predominate, and the dielectric anisotropy ($\Delta\varepsilon = \varepsilon_1 - \varepsilon_2$) will be positive. The dielectric anisotropy of the azoxybenzene derivative *(22)* amounts to −0.2, and that of the azobenzene analog *(21)* +0.2. That the ether oxygen in *(22)* also makes a crucial contribution to the permanent transverse dipole moment is apparent from a comparison of the dielectric anisotropy of *(22)* with that of *p,p'*-di-*n*-butylazoxybenzene (+0.19)[69,90].

Nitrile groups in one of the *para* positions increase the dielectric anisotropy. Thus a dielectric anisotropy of +14 was recently reported[91] for the eutectic system comprising 2/3 *(23)* and 1/3 *(24)*, m.p. −30 °C, clearing point 62 °C.



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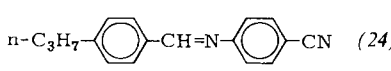


(24)

The phase diagrams of binary nematic systems display the known depression of freezing point which leads in

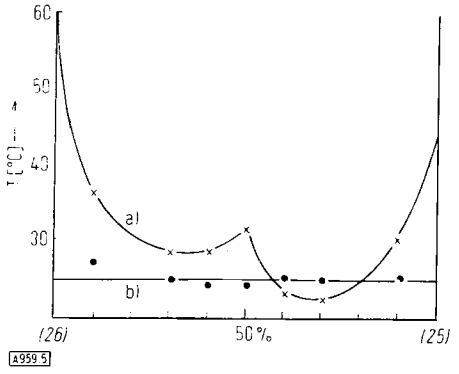
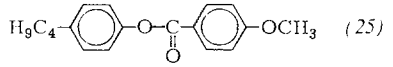


Fig. 5. Phase diagram of a binary mixture of the phenyl benzoates (25) and (26): a) melting points, b) clearing points.

some cases to very low-melting eutectics. Since the melting temperature of such mixtures can be calculated by the classical van't Hoff-Schröder-Van Laar formula under certain conditions, it is also possible to calculate the eutectic composition of binary systems[92].



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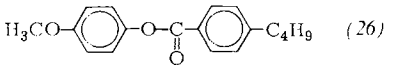
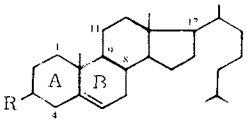


(26)

The clearing points lie practically on a straight line between the clearing points of the two pure components. Figure 5 depicts a phase diagram of the monotropic nematic compounds (25) and (26) which form an enantiotropic nematic eutectic. The 2:1 composition of the eutectic, also found in the (23)/(24) mixture, is typical of numerous binary nematic systems[93].

3.3. Molecular Structure of Cholesteric Compounds

Cholesteric mesophases occur primarily in cholesterol derivatives of type (27) in which the hydroxyl group in position 3 is esterified with aliphatic[65] or aromatic[94,95] carboxylic acids, hydrogen carbonates[96], or inorganic acids[65]. Here, too, long-chain substituents enhance the tendency to form enantiotropic smectic phases which undergo transition to cholesteric mesophases at elevated temperatures.



(27)

The only hydrogenation product of cholesterol able to form esters having cholesteric properties is 5α-cholestan-3β-ol. In the 5β compound, rings A and B are *cis* to each other, thus ruling out the planar conformation which is also an important structural feature of the cholesteric mesophase[97,98]. Studies by *Pohlmann et al.*[99] and *Atallah et al.*[100] on the influence of the position of a double bond in steroids and triterpenes on the formation and type of mesophases revealed that mesophase formation is not supported by a C-1, C-4, or C-8 double bond in the steroid molecule, whereas a double bond between C-9 and C-11 permits a cholesteric phase. The nature and length of the 17β side chain also exert a considerable influence on the mesomorphic behavior of the molecule[101]. Accordingly, extensive variations of the cholesterol molecule are possible without loss of liquid-crystalline properties. It is therefore hardly surprising that cholesteric mesophases have also been found for derivatives of other naturally occurring steroids such as sitosterol[65] or 9,13-cyclopropane triterpenes[102]. However, nonsteroidal compounds of nematogenic structure can also form cholesteric mesophases provided that they contain optically active substituents[65,103]. It appears that an asymmetric center suffices to impart to the nematogenic molecules the helical arrangement necessary for formation of a cholesteric mesophase.

4. Use of Nematic Liquid Crystals in Electrooptic Display Devices

Application of electric fields of a few hundred to several ten-thousand V/cm can induce changes in the state of order of thin nematic liquid-crystalline films. These changes in order are observable as changes in optical properties such as transparency, light scattering, birefringence, or color. Such electrooptical effects can be observed and utilized in a set-up consisting of two conducting glass plates coated on the inside with a transparent SnO_2 or In_2O_3 layer and between which there is a 5–50 μm uniformly

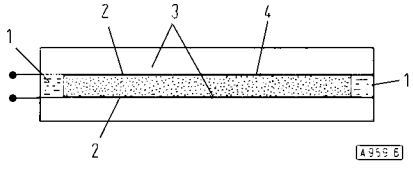


Fig. 6. Section through a liquid crystal display device. 1, separating foil; 2, electrode layer of SnO_2, In_2O_3, or a similar substance; 3, glass plate; 4, nematic phase (5–25 μm).

oriented nematic film (Fig. 6). Thinner layers are difficult to produce and thicker ones exhibit strong light scattering.

4.1. Orientation of Nematic Liquid Crystals at Interfaces

In cells of the above type the liquid crystal molecules can adopt orientations with their long axis either perpendicular or parallel to the walls (Figs. 7a and 7b). The former case is described as a homeotropic phase or orientation, and the latter as a homogeneous one. The orientation of the molecules at the interface is transmitted to the internal molecules by dispersive interaction. The methods used for production of uniformly oriented layers are still largely empirical.

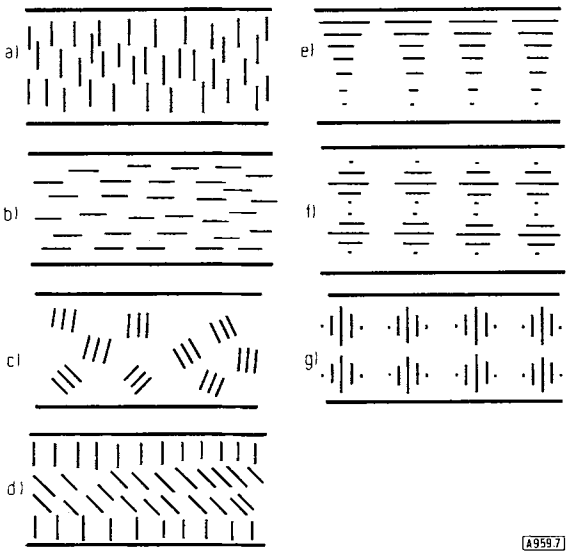


Fig. 7. Possible orientations of thin liquid crystalline layers; a, homeotropic; b, homogeneous; c, disordered, dynamic scattering; d, deformed homeotropic; e, twisted homogeneous; f, cholesteric planar; g, cholesteric focal conic structure.

The homeotropic orientation (Fig. 7a) can be achieved by treatment of the glass plates with an ethanolic lecithin solution[104] or by addition of polyamide resins[105] or quaternary ammonium salts[106] to a nematic liquid crystal. Some commercially available nematic phases are already doped so as to automatically adopt a homeotropic orientation[107].

The homogeneous orientation (Fig. 7b) can be brought about by unidirectional rubbing of the electrode surfaces with polishing cloths[108] or pastes containing diamond dust[109]. Such treatment produces submicroscopic grooves parallel to which the molecules adjacent to the interface become aligned. As demonstrated by *Berreman*[110], any other orientation of these molecules would incur expenditure of additional elastic energy. Homeotropic or homogeneous orientations are reported to be inducible according to choice by dipping the electrodes into solutions of *N*-hexadecyl-*N*,*N*,*N*-trimethylammonium bromide depending on the concentration and rate of immersion[111]. More reproducible homogeneous phases are obtained at electrode surfaces whose conducting surface has been condensed on at an angle of about 85° [112].

4.2. Interactions between Electric Fields and Nematic Liquid Crystals[90, 113]

Three kinds of electrooptical effect are known to occur in liquid crystals, *viz.* dielectric, piezoelectric, and electrohydrodynamic effects. The first two arise solely from the influence of electric fields without simultaneous participation of charge transport and are known collectively as field effects. They result from static, so-called dielectric deformation of the existing orientation of the liquid crystals and become operative above a certain threshold voltage that, for dielectric effects, is independent of the layer thickness but dependent upon the dielectric anisotropy and the splaying, bending, or twisting of the liquid crystalline layer[114, 115].

Nematic crystals exhibiting positive dielectric anisotropy (cf. Section 3.2)—this applies to molecules having a strong electric dipole in the direction of the long molecular axis—align their long axes parallel to the direction of the field under the influence of a DC or AC potential. This homeotropic orientation is further promoted by a flow of charge carriers between the electrodes.

Field effects are more complicated in the case of nematic substances having negative dielectric anisotropy[29, 90]. For small AC potentials (5—10 V depending on conductivity and thickness of sample) a static deformation of the layer takes place, irrespective of whether it was originally homogeneous or homeotropic. A system of largely parallel striations is observed under a polarizing microscope. The line textures are called Williams domains after their discoverer[116–118]. The long axes of the molecules are arranged substantially parallel to the surface of the electrodes.

The same phenomenon is observed at higher potentials as long as their frequency is in excess of the cut-off frequency. This term denotes the frequency at which the preferred orientation of the liquid crystalline molecules due to the field is no longer subject to interference by migration of charge carriers[90, 119]. It is dependent upon the conductivity of the material and lies below 30 Hz for liquid crystals having $R > 10^{12}$ ohm cm and above 30 Hz for those with $R < 10^{12}$ ohm cm.

With potentials having frequencies lying below the cut-off frequency, fields in excess of about 10 kV cm^{-1} lead to perturbation of the molecules oriented parallel by the field owing to the flow of charge carriers between the electrodes, thus displacing the molecules from their stable equilibrium positions and destroying the overall optical homogeneity except for very small residual regions which act as scattering centers for light (Fig. 7c). Viewed under a polarizing microscope these small regions are seen to undergo vigorous turbulent motion. Macroscopically, this turbulence manifests itself in a sharp increase in scattering, conveying the impression that a transparent glass is transformed into a frosted glass on application of the DC or AC potential. This phenomenon is known as "dynamic scattering"[120].

4.3. Electrooptical Display Devices Employing Nematic Liquid Crystals

Most of the commercially available displays utilizing liquid crystals are currently based on the dynamic scattering effect. In addition, increasing use is being made of pure field effects for electrooptical applications.

4.3.1. Displays Based on Dynamic Scattering[121, 122]

Dynamic scattering cells can be constructed in a transmission or a reflection mode. In the former case both electrodes are transparent, and in the second the rear electrode is a mirror. All systems of this kind are characterized by their flat construction (2—3 mm thick), high contrast ratios in excess of 100:1 (the best contrast being obtained with homeotropic or homogeneous phases), low driving voltages

between about 20 and 30 V, and minimum power consumption of at most 500 $\mu W/cm^2$ of active display area.

Fig. 8. Example of a liquid crystal display based on dynamic scattering.

The lifetime of such display systems depends upon whether they work with AC or DC. For AC operation values in excess of 10000 operating hours are reported. DC operation often leads to gradual deposition of the ions required for dynamic scattering so that the conductivity often drops below the threshold potential for dynamic scattering. This effect can be suppressed by addition of less than 1% of a charge-transfer acceptor, *e.g.* chloranil, which lowers the threshold potential by a factor of 2[123].

The switching times depend on the layer thickness of the nematic phases, the driving voltage, the conductivity, the dielectric anisotropy, and the viscosity. The following values are typical for the standardized commercial nematic material[107] used for dynamic scattering applications (conductivity: 4×10^{-10} to 10×10^{-10} ohm^{-1} cm^{-1}):

T_r (raise time):	18 to 28 ms
T_d (decay time):	25 to 50 ms

(measuring conditions: $d = 10\,\mu m$, $U = 25$ V/50 Hz, SnO_2 electrodes)

Apart from digital and analog display of measured values, time of day, and computer and process data (Fig. 8), display systems with nematic liquid crystals are suitable for use in, *e.g.* remotely controlled flight timetables, windows of variable transmission, or advertising displays. Unlike conventional luminous display they become more and more legible as the brightness of the environment increases.

4.3.2. Display Devices Based on Electroelastic Deformation of Vertically Aligned Nematic Layers (DAP Effect)

Homeotropically oriented layers of negative dielectric anisotropy readily undergo elastic deformation on application of an electric field parallel to the principal optical axis of the molecules, leading to a displacement from their perpendicular orientation (Fig. 7d). This effect is designated as deformation of vertically aligned phases or in abbreviated form as the DAP effect[124, 125]. The degree of deformation depends on the applied voltage. In the extreme case the molecules flip out of their homeotropic into a homogeneous orientation. The potential required for displacement of the molecules lies in the range 5—10 V and is thus much lower than the corresponding driving voltage of 20—30 V for dynamic scattering. The occurrence of dynamic scattering during deformation is avoided by the use of high resistance liquid crystals and AC potentials having frequencies above the cut-off frequency.

Homeotropic liquid crystalline layers behave like optically positive, uniaxial crystals. Light entering the crystals in the direction of the optical axis emerges unchanged. If such a liquid crystalline layer is situated between crossed polarizers the overall system cannot transmit light and thus appears black.

If the liquid crystalline layer is deformed by application of an electric field, the angle between the optical axis of the liquid crystal and that of the incident light, *i.e.* the angle of incidence, differs from zero and birefringence occurs. Under these conditions, and using parallel light the intensity (I) of the emerging light depends on the phase difference δ between the ordinary and the extraordinary ray as shown in eq. (1).

$$I = I_0 \sin^2(\delta/2) \tag{1}$$

The phase difference itself varies with the difference between the refractive index of the extraordinary ray (n_e) and the ordinary ray (n_o) according to eq. (2).

$$\delta = \frac{2 \times \pi \times d}{\lambda} \Delta n, \quad \Delta n = n_e - n_o \tag{2}$$

For a given layer thickness d and wavelength λ (monochromatic light) the angle of incidence can be varied at will between 0 and 90° *via* the deformation of the homeotropic phase by the applied voltage. It is thus possible to switch the system from opacity to transparency, *i.e.* from dark to light. Contrast ratios in excess of 500:1 are perfectly feasible[126].

4.3.3. Display Devices Based on an Electroelastic Deformation of Homogeneous Nematic Layers (Fréedericksz Effect)

Homogeneously oriented nematic liquid crystals of positive dielectric anisotropy can be reoriented homeotropically by application of a DC or AC field perpendicular to the long molecular axis. This effect, the counterpart of the deformation of vertically aligned phases, produces the same observable effect as the latter and was described by *Fréedericksz* as long ago as 1933[127]. Such a layer between crossed polarizers can be switched from transparency to opacity, *i.e.* from light to dark.

4.3.4. Display Devices Based on Electroelastic Deformation of Twisted Nematic Layers (Schadt-Helfrich Effect)

Homogeneous phases can also be obtained in which the liquid crystals exhibit a preferred orientation differing by 90° between the opposite electrode surfaces[114] (Fig. 7e). Polarized light passing through such a twisted layer

is accordingly rotated through 90°, and between crossed polarizers the system is transparent. An electric field can induce homeotropic reorientation of the phase if the molecules possess a positive dielectric anisotropy (Fig. 7b). Polarized light is then unaffected and the system is opaque, appearing black. This effect, discovered by *Schadt* and *Helfrich*[114], yields high contrasts, and exhibits threshold potentials of less than 1 V[91], driving voltages of 2—5 V[128], and power consumptions of 1—50 $\mu W/cm^2$.

4.4. Electrooptical Effects Based on Textural Changes in Liquid Crystals

Addition of a chiral compound to a nematic liquid leads to two further effects, depending upon the anisotropy, designated as memory and transparency effects. Both arise from light scattering by disordered phases. However, since they represent stable textures and are not due to turbulence within small liquid crystalline regions, they differ fundamentally from dynamic scattering.

4.4.1. Memory Effect in Liquid Crystals[48, 56, 129]

Mixtures of a nematic liquid crystal of negative dielectric anisotropy and a cholesteric[130] or non-liquid crystalline chiral substance such as L-menthol[131] can be used to prepare thin films whose order corresponds to the planar cholesteric texture (Fig. 7f). Application of a DC potential transforms this phase into a strongly deformed, light-scattering phase exhibiting a focal conic texture (Fig. 7g) and having randomly oriented helical axes in the individual subregions. After removal of the applied potential the disordered phase reverts to the original ordered state within minutes or days, depending on the concentration of the chiral component (1—10%)[132]. An AC potential of 50 to 100 V whose frequency must exceed the cut-off frequency and is generally above 700 Hz, can reconvert the disordered into the ordered phase within milliseconds[133]. This reversible change of texture permits the construction of an optical memory device in which information can be recorded with an DC potential and erased with an AC potential.

4.4.2. Transparency Effect in Liquid Crystals[134]

For mixtures comprising 30—90% of a nematic liquid crystal of *positive* dielectric anisotropy and 70—100% of a cholesteric liquid crystal, a disordered molecular arrangement, or focal conic texture, is the most stable possibility. Such a liquid crystalline film therefore exhibits pronounced light scattering. An AC potential can transform the disordered phase into an unstable homeotropically oriented, transparent layer which reverts to the disordered state when the potential is removed. The switching times depend, *inter alia*, on the thickness of the layer, the dielectric anisotropy, and the mixing ratio of nematic to cholesteric liquid crystals, and lie below 10 ms; the AC potentials required are between 30 and 100 V.

4.5. Production of Colors with Nematic Liquid Crystals

Apart from black-and-white contrasts, nematic liquid crystals can also be used for generating colors by virtue of interference phenomena in homogeneous or homeotropic layers or of reorientation of dichroic dyes embedded in a liquid crystalline matrix.

4.5.1. Colors from Tunable Domains

Homogeneously or homeotropically oriented layers (3 to 6 μm thickness) of high resistance ($> 10^{12}$ ohm cm) nematic liquid crystals with negative dielectric anisotropy exhibit Williams domains (Section 4.2) when an applied potential alternates at a frequency in excess of the cut-off frequency. The width of the domains can be reduced by a factor of 10 from *e.g.* 10 to 1 μm if the applied potential is raised by the same factor, *e.g.* from 10 to 100 V. Such liquid crystalline layers therefore behave as a tunable optical diffraction gratings which, being phase gratings, are highly efficient. If a directional filter which only transmits light of a particular diffraction angle is placed behind one of these gratings and white light shone onto the set-up, any desired spectral color can be obtained by changing the applied potential[135–137].

4.5.2. Colors Produced by Reorientation of Aligned Phases (DAP and Fréedericksz Effect)

If white light is used instead of monochromatic light with the set-up described in Sections 4.3.2 and 4.3.3, then according to eq. (2) the phase difference between the ordinary and the extraordinary ray occurring on deformation of the homeotropic or homogeneous phase depends not only upon the angle of incidence but also upon the wavelength. Interference between these two rays thus leads to the appearance of Newtonian colors. For a given direction of observation any desired spectral color can be obtained by variation of the applied potential.

4.5.3. Colors Produced by Dichroic Liquid-Crystalline Color Switches

Dyes exhibiting differential absorption of polarized light in the directions of the individual axes are called dichroic. Representatives of this group include indophenol blue, alizarin, and oil yellow. Since the guest molecules dissolved in a nematic liquid crystal frequently adopt the same orientation as the liquid-crystalline host molecules and are reoriented with the latter by electric fields, dichroic dyes can be utilized in the production of color switches[138–140] that can be tripped from colored to colorless or *vice versa* (Fig. 9).

A *homogeneously* oriented film (Fig. 9a) of a nematic liquid crystal of *positive* anisotropy doped with 1—2% of a dichroic dye absorbs only light polarized in the direction of the transition moment. Such a system is therefore colored. If a doped liquid crystalline layer is aligned homeotropically by a DC or AC potential (Fig. 9b) interaction no longer occurs between the chromophore and the incident light and the system is colorless.

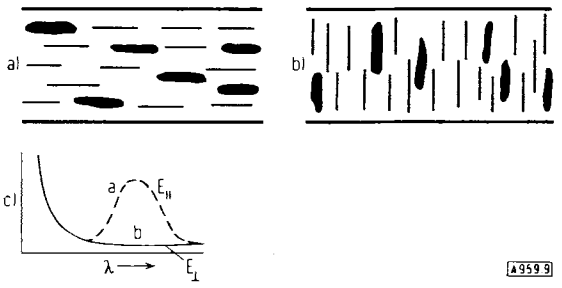


Fig. 9. Inclusion of dichroic dye molecules in a nematic layer: a, absorbing; b, nonabsorbing; c, absorption curves.

Conversely, a corresponding *homeotropic* layer of a nematic liquid crystal of *negative* anisotropy is colorless in its quiescent state and becomes colored when it undergoes homogeneous reorientation. A color switch of this kind also functions with unpolarized light. Since the driving voltages required are of the same order as those required for dynamic scattering the latter type of color switch, in contrast to the former, requires AC potentials having frequencies in excess of the cut-off frequency for dynamic scattering.

4.6. Piezoelectric Effect in Nematic Liquid Crystals

The phenomenon of piezoelectricity as known for natural electrets such as quartz or tourmaline and which nowadays finds wide technical application in quartz crystal oscillators was first detected in liquid crystals in 1972[141].

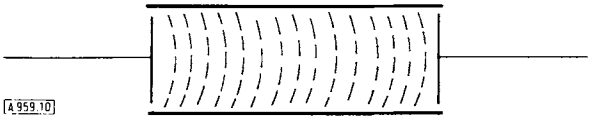


Fig. 10. Distorted homeotropic layer exhibiting piezoelectric properties.

If an electric potential is applied perpendicular to the molecular orientation of a homeotropic layer of nematic liquid crystals of negative dielectric anisotropy, the orientation of the liquid crystals becomes distorted in the direction of the field (Fig. 10). The liquid crystalline layer which was originally isotropic to the incident light striking it parallel to the preferred orientation becomes anisotropic due to the distorted molecular arrangement and thus birefringent. This bending or piezoelectric effect leads, *e.g.* for layer thicknesses of *ca.* 100 µm and field strengths of 100 V/cm, to an optical phase difference between the ordinary and extraordinary refractive rays of 300 Å.

5. Liquid Crystals as Anisotropic Solvents for Molecular Spectroscopy

Anisotropic spectroscopic molecular properties, *e.g.* polarization of an electronic or vibrational transition in the UV or IR or the magnitude of a direct intramolecular dipole-dipole interaction in NMR and ESR, can only be observed with oriented molecules. Corresponding studies can be performed both in the solid state and in liquid crystalline solvents[3, 142–145].

Since the molecules dissolved in a liquid crystal are frequently aligned parallel to the preferred orientation of the principal axis of the liquid crystal it becomes possible to study not only the anisotropic molecular constants of the liquid crystal itself but also those of the molecules dissolved therein.

Planar or elongated molecules can be dissolved in nematic liquid crystals in concentrations up to 30 mol-% without destroying the liquid crystalline state. This limiting value is frequently much lower for spherical molecules. The dissolved molecules usually exhibit a lower degree of order than the solvent molecules. Since the clearing point is invariably lowered more than the melting point the nematic range is significantly narrower than that of the pure solvent. Spectroscopic studies therefore require liquid crystals with wide mesophase ranges, which should be liquid crystalline at room temperature to facilitate experimental work.

5.1. Liquid Crystalline Solvents in Optical Molecular Spectroscopy

Determination of the polarization of absorption or fluorescence bands is usually performed with single crystal sections. High intensity bands require single crystal sections less than 1 µm thick whose preparation and handling is not easy and sometimes even impossible. The alternative procedure of working with non-absorbing single host crystals or with stretched plastic films[146–148] into which the sample under study has been previously incorporated is complicated and again sometimes impossible. In contrast, nematic liquid crystalline solvents permit the recording of polarization spectra in the same simple manner in which spectra are measured in isotropic solvents.

Investigation of the polarization of a transition with the aid of homogeneously oriented liquid crystalline layers requires use of linearly polarized light. Measurements in homeotropic phases, however, also permit the direction of the transition moment to be determined without polarized light, the spectrum of the nematic solution being recorded first and then that of the isotropic solution above the clearing point. The difference in intensity between the individual bands allows unambiguous assignment of their polarization[149].

5.1.1. Use of Liquid Crystals in Absorption and Fluorescence Spectroscopy

The intrinsic absorption of nematic liquid crystals of the Schiff base, azoxybenzene, or phenyl benzoate type preclude their use as solvents for recording polarized absorption of fluorescence spectra except for molecules whose spectra lie above 350 nm[150, 151]. Compensated cholesteric liquid crystals (see Section 2.3), on the other hand, represent nematic solvents which transmit light above 250 nm and which can readily be supercooled to give vitreous solutions by quenching[36, 152–154].

While the degree of order S of dissolved molecules, and its temperature dependence, can also be ascertained from

polarized absorption spectra[155-157], these quantities cannot generally be obtained from the corresponding fluorescence spectra since the polarized fluorescence of the dissolved molecules is anisotropic in the various axial directions, *i.e.* may be quenched to varying extents. Hence the fluorescence intensity measured is no longer solely dependent on the molecular orientation[158].

5.1.2. ORD and CD in Nematic Solvents

On dissolution of chiral compounds in a nematic solvent the solute molecules induce a helical ordering of the liquid crystalline molecules and thus transform the nematic liquid into a cholesteric phase which exhibits optical rotatory dispersion (ORD) and circular dichroism (CD)[41]; 1—2 mol-% of the chiral compound suffice to effect this transition. The effect is caused both by asymmetric molecules such as L-menthol[159] and by dissymmetric structures such as diazacycloctatetraene derivatives[41], the sense of rotation of the helix depending upon the chirality of the solute molecules. Since the induced specific rotation of the cholesteric liquid crystalline solution can far exceed 1000° and is hence three orders of magnitude larger than that of the molecular compounds or molecules dissolved in isotropic solution, these effects, which were first described by *Stegemeyer et al.*, are suitable for detecting small amounts of optically active or chiral molecules having very low optical activities.

5.1.3. Induction of Optical Activity by Cholesteric Solvents

The complementary phenomenon, *i.e.* induction of a Cotton effect within the absorption bands of achiral molecules with the aid of a cholesteric liquid crystalline solvent, has meanwhile also been established[160-164]. Here the helical structure of the cholesteric solvent is impressed upon the spatial arrangement of the dissolved molecules, leading to molar amplitudes of the induced rotatory dispersion of the order of 10^7 deg cm^2. These values thus exceed *e.g.* those of the pronouncedly chiral compound hexahelicene (8.62×10^5 deg cm^2) by several orders of magnitude. *E. Sackmann*[165] and *Saeva*[166] have developed a method of establishing the polarization of the pertinent electronic transition of the dissolved achiral molecule from the sign of the induced Cotton effect. The method clearly supplements the techniques hitherto available for determining the direction of electronic transition moments in molecules.

5.1.4. IR Spectroscopy in Nematic Solvents

Owing to their numerous absorption bands nematic liquid crystals find only limited use as anisotropic solvents for recording polarized IR spectra, which differ from the non-polarized IR spectra only in the intensities of analogous bands. This intensity difference which is known as infrared dichroism permits determination of either the degree of order[156,157,167] or the vibrational class of the individual bands of the dissolved molecule[151,168]. The method has been used primarily for investigation and assignment of —C≡N, —C=O, —C≡C—, and =C=O stretching vibrations.

5.1.5. IR-ORD in Nematic Solution

The theory of rotatory dispersion predicts that Cotton effects should also occur in the infrared. However, the amplitudes of these anomalies are four orders of magnitude smaller for vibrational than for electronic transitions. Nevertheless, as *Schrader* and *Korte*[169] were able to show for the first time, Cotton effects also occur in the IR with amplitudinal values of several thousand deg per mm when chiral molecules are dissolved in nematic solvents. The frequencies at which these IR Cotton effects are observed agree, as in the UV, with the absorption bands of the liquid crystal but not with those of the dissolved molecule.

5.2. NMR Spectroscopy in Nematic Solvents[3,142,143]

Proton and fluorine nuclear magnetic resonance spectroscopy in nematic solvents is already a routine method for determining bond angles and relative bonding distances in proton deficient molecules and has been treated in detailed reviews[170-172]. Advances in the field of Fourier transform NMR spectroscopy have meanwhile facilitated measurements on nuclei of low sensitivity and low natural abundance, *e.g.* ^{13}C-NMR spectra, without preliminary isotopic enrichment[173]. If the degree of order of the solute molecules is known, the direct ^{13}C-^{1}H nuclear spin coupling constants $D_{^{13}C-^1H}$ obtained from these spectra, which at 1 500 Hz are larger than the indirect ^{13}C-^{1}H coupling constants $j_{^{13}C-^1H}$ by a factor of 10, can be utilized for calculating not only the H—C—H bond angles but also C—H bond lengths. In contrast, the analogous anisotropic proton spectra yield only relative internuclear distances *via* the direct ^{1}H-^{1}H coupling constants. Because of the numerous possible dipole couplings in molecules containing many protons the resonances exhibit such extensive splitting, as in anisotropic proton spectra, that analysis is no longer possible. The application of this method is therefore limited to small molecules.

5.3. ESR Spectroscopy in Liquid Crystals

ESR spectra in liquid crystalline solvents provide extremely valuable information, also for the preparative chemist[174-176]. Both liquid crystalline[175,177] and glassi[177,178] nematic, supercooled compensated cholesteric[153] and also smectic liquid crystals[179,180] are used in these studies. The direct dipole-dipole interaction between the unpaired electrons of a multiple radical which is averaged to zero by Brownian motion in isotropic solution is retained in liquid crystalline solution and appears—*e.g.* as a triplet for a biradical—alongside the hyperfine splitting. Thus an ESR spectrum in liquid crystalline solution, in contrast to the results obtained in isotropic solution, provides a clear-cut answer to the question of how many unpaired electrons a radical contains[174,184]. It also permits calculation of the concentration, and its temperature dependence, of multiple radicals[181].

Highly complex ESR spectra can be considerably simplified by electron-nucleus double resonance experiments

(ENDOR). Low-melting azoxybenzene derivatives have proved particularly suitable for such studies[182].

5.4. Mössbauer Spectroscopy in Smectic Phases

One of the few applications of smectic phases has recently been found in Mössbauer spectroscopy[183–187]. The possibility of translational molecular motion in all three spatial directions in nematic phases rules out their use as matrices for Mössbauer measurements. Recoilless γ-resonance is feasible, however, in smectic solvents where translational motion is permitted within a molecular layer in the direction of the long molecular axis but not in a perpendicular direction. Measurement of Mössbauer spectra in a smectic rather than a solid matrix has the advantage of simplified sample preparation, provided the substance under study is sufficiently soluble. The intensity of the spectra is albeit lower than in crystalline matrices.

6. Outlook

Although it is only in the last 10 years or so that the potential technical applications of nematic liquid crystals have been studied in depth, these substances now occupy a strong position in the field of electrooptics in such applications as digital indicators for electronic clocks, table-top calculators, and measuring instruments; in the near future we shall see their application in remote controlled traffic signs and information boards, vehicle instrument panels, special window panes, in which the degree of light penetration may be controlled, and camera shutters. Looking further into the future, we can also anticipate optical memory devices and flat large area color television screens.

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Reactive Monomeric Carbonic Acid Derivatives

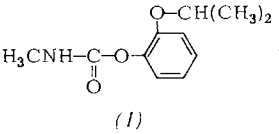
By Engelbert Kühle[*]

Monomeric carbonic acid derivatives that can react by addition or substitution are systematically discussed according to the three tabular surveys A, B, and C, from which a principle for the classification of carbonic acid derivatives can be readily deduced. For each type of compound, a brief description is given first of the principal syntheses and then of the reactions, and the heterocycles obtainable by addition, disubstitution, or coupled addition-substitution are also considered. The carbonic acid derivatives discussed can be synthesized from very simple and in most cases cheap base chemicals.

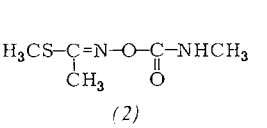
Introduction

The derivatives of carbonic acid are usually discussed only briefly in textbooks of organic chemistry, though carbonic acid chemistry actually offers the synthetic worker a multitude of possibilities for the synthesis of new compounds, and carbonic acid derivatives have a very wide range of uses in industrial chemistry.

The industrial importance of carbonic acid chemistry is clear from the following brief enumeration of its uses. Urea-formaldehyde and melamine resins have been in use for a long time; polycarbonates and polyurethanes are modern plastics used *e.g.* as foams, paint components, and products with rubbery properties. Cyanuryl chloride is used as a reactive component for dyes and as a starting material for herbicides. Arylalkylureas and *N*-arylcarbamic esters also have herbicidal properties, while aryl *N*-methylcarbamates, *e.g. (1)*, and *N*-methylcarbamidoximes, *e.g. (2)*, are used as cholinesterase inhibitors for the control of insects.



(1)



(2)

The fungicides used in agriculture include the dithiocarbamic acids; *N*-trihalomethylthio compounds, which can also be regarded as carbonic acid derivatives, are used for the same purpose. Very many carbonic acid derivatives are found in drugs. The range extends here from the old-established barbiturates to the modern antidiabetics based on sulfonylureas. A number of sulfonamides used in pharmaceutical applications are also based on carbonic acid derivatives. Finally, carbonic acid structures are found in complicated natural products, *e.g.* in antibiotics (streptomycin) and vitamins (folic acid), and as essential components of the nucleic acids (guanine, cytosine, thymine).

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The purpose of the present article is to make the reader more familiar with low molecular weight carbonic acid chemistry through the system used here. To keep matters simple, the article deals only with carbonic acid compounds that can react by addition or chlorine substitution. Other halogens are considered only in special cases.

The tabular surveys at the beginning of each section are arranged in such a way that the elements or groupings of the 7th to the 5th main groups of the periodic system appear from top to bottom in the vertical direction and from left to right in the horizontal direction.

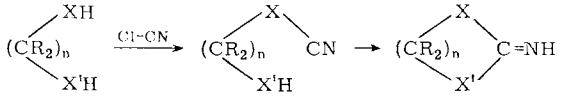
A. Compounds Containing a CN Triple Bond

		I— CN
1	Cl—	Cl—CN
2	RO—	RO—CN
3	RS—	RS—CN
4	ClS—	ClS—CN
5	R_2N—	R_2N—CN

A 11. Cyanogen Chloride

Cyanogen chloride is generally available as a 7% aqueous solution or as the anhydrous product in gas cylinders. It is synthesized by chlorination of hydrocyanic acid or alkali metal cyanides in water[1] or in inert organic solvents[2].

Cyanogen chloride can add to CC multiple bonds in the same way as the halogens, but only in the presence of $AlCl_3$ as a catalyst[3]. Conversely, it can add a wide range of electrophilic agents across its CN triple bond, in some cases with rearrangement, examples being the addition of chlorine[4, 5], phosgene[6], and acyl chlorides[7, 8] to form isocyanide dichlorides (B I4) and of SO_3 to form chlorosulfonyl isocyanate[9] (B II4). Nucleophilic substitution of the chlorine in cyanogen chloride leads with phenols to esters of cyanic acid (A I2), with thiols to esters of thiocyanic acid (A I3), and with amines to cyanamides (A I5). Numerous five-membered and six-membered heterocycles can be synthesized by substitution followed by addition to suitable 1,2- and 1,3-disubstituted nucleophiles[10].

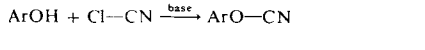


n = 2, 3

X, X' = O, S, NR'

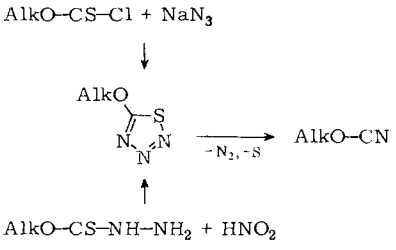
A 12. Esters of Cyanic Acid

The synthesis of the cyanates, which are isomeric with the isocyanates (B II4), has been achieved only during the last few years. Aromatic cyanates can be obtained by reaction of phenols with cyanogen chloride in the presence of a base[11]. The yields are very good.



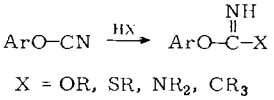
The only aliphatic cyanates that can be obtained by this method are the esters with strongly acidic alcohols, such as trichloroethyl cyanate[12].

Aliphatic cyanates are generally obtained by thermolysis of 5-alkoxy-1,2,3,4-thiatriazoles[13–15].



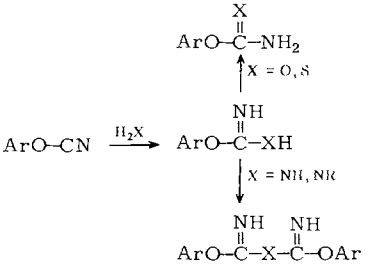
The alkyl cyanates are relatively unstable, since they readily isomerize to isocyanates or trimerize[15]. Nucleophilic substitutions have been achieved only on the alkyl cyanates, using nucleophilic anions (I^-, SCN^-, OCN^-)[16].

The addition of nucleophilic compounds, which has occasionally also been carried out with alkyl cyanates[16], has been extensively studied for aryl cyanates[11]. This reaction, which proceeds under mild conditions and in many cases with catalysis by acids or bases, often leads to further reaction products, depending on the other reactant (cyclizations, transfer of cyano groups). The addition of nucleophiles with a proton on the O, S, or N atom and of CH acids follows the indicated general scheme in the first step. A C—C linkage thus occurs with CH acids.

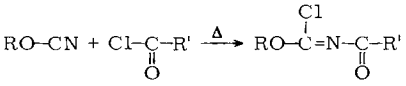


X = OR, SR, NR_2, CR_3

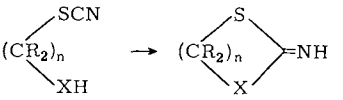
When water or hydrogen sulfide is used, the adducts isomerize to form esters of carbamic or thiocarbamic acid, while ammonia and primary amines lead to 2:1 adducts.



The addition of acyl chlorides to cyanic esters, which proceeds only at high temperatures, leads to *N*-acyliminocarbonic ester chlorides[17]. This reaction also takes place with sulfenyl chlorides.



Numerous heterocycles can be synthesized by further reactions, particularly with bifunctional systems or directly by 1,3-dipolar additions (with hydrazoic acid, diazomethane, nitrile oxides, nitrile imines)[11].

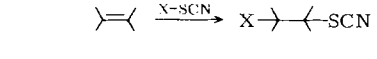


n = 2, 3
X = O, S, NR

A 13. Esters of Thiocyanic Acid

The thiocyanates are isomers of the thermodynamically more stable isothiocyanates (B III4), and can be rearranged into the latter in many cases by heating. Numerous methods are known for the synthesis of thiocyanates, but their application is limited in most cases to certain types.

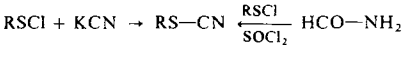
Aliphatic thiocyanates are obtainable by the action of alkylating agents on alkali metal thiocyanates, but depending on the nature of the aliphatic residue, isothiocyanates may also be formed as by-products or as the principal products[18,19]. The addition of dithiocyanogen and of thiocyanogen chloride to CC multiple bonds leads to 1,2-bis(thiocyanates)[20] and to 2-chloro-1-thiocyanates respectively (cf. A I4).



X = -SCN, Cl

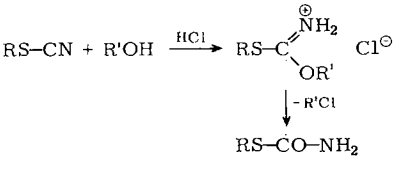
With both reagents, aromatic compounds (phenols, amines) undergo electrophilic ring substitutions with formation of aryl thiocyanates[20,21] (cf. A I4). Another specific synthesis for aryl thiocyanates is the reaction of alkali metal thiocyanates with diazonium salts in the presence of copper salts (Gattermann-Sandmeyer synthesis)[22].

Two methods with a wider range of applications start with sulfenyl chlorides or thiols. The synthesis from sulfenyl chlorides and alkali metal cyanides[23] can be modified by reaction of sulfenyl chlorides with formamide in thionyl chloride[24].



Finally, in analogy with the synthesis of the cyanates (A I2), thiolates or thiols[25,26] react with cyanogen chloride to form thiocyanates.

The thiocyanates are also related to the cyanates in their reaction behavior. Thus alcohols can be added to the CN triple bond in the presence of hydrogen chloride, though the number of examples known in this case is smaller[27].

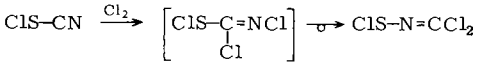


Cyclizations by intramolecular addition of suitable nucleophilic groups in position 2 or 3 lead to five-membered or six-membered heterocycles[28].

A 14. Thiocyanogen Chloride

Like dithiocyanogen, thiocyanogen chloride may be regarded as a pseudohalogen, which is polarized into Cl^- and SCN^+. The compound, which is reasonably stable only in cold solution, can be obtained by chlorinolysis of dithiocyanogen in a chlorine-resistant solvent such as chloroform[29]. Instead of starting with dithiocyanogen, one can obtain thiocyanogen chloride by direct chlorination of alkali metal thiocyanates[30].

Excess chlorine adds to the CN triple bond with rearrangement to form chlorosulfenyl isocyanide dichloride ("thiocyanogen trichloride")[31,32].

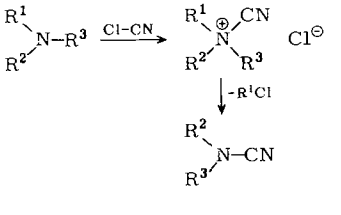


As a pseudohalogen, thiocyanogen chloride adds to olefins under mild conditions to form 2-chloro 1-thiocyanates[29].

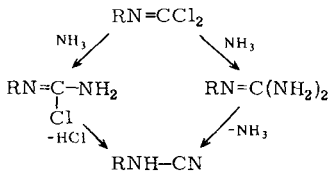
As was mentioned in Section A I3, thiocyanogen chloride can also convert aromatic compounds (amines, phenols, phenol ethers, higher aromatic hydrocarbons) into aryl thiocyanates, and does so more effectively than dithiocyanogen[30,33].

A 15. Cyanamides

Unsubstituted cyanamide[34], which is obtainable from calcium cyanamide, can be converted into alkylcyanamides by alkylation, as can the alkali metal cyanamides[35]. A general method for the synthesis of substituted cyanamides is based on the reaction of cyanogen chloride with primary or secondary amines and with hydrazines and hydrazides at low temperatures[36]. Even tertiary amines, which undergo a von Braun degradation with cyanogen chloride, with elimination of alkyl chloride, are suitable for this purpose[37].

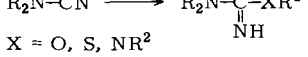


Monosubstituted cyanamides can also be obtained from isocyanide dichlorides (B I4) and ammonia *via* the chloroformamidines or guanidines[38].

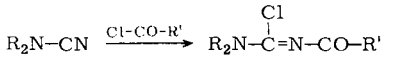


Finally, thioureas and isothioureas can be converted into cyanamides by elimination of hydrogen sulfide or thiols[39]. Monosubstituted cyanamides, as weakly basic compounds, are acylated by carbonyl chlorides, sulfonyl chlorides, esters of chlorocarbonic acid, acid anhydrides, isocyanates, *etc.*[36].

Like cyanates and thiocyanates, the cyanamides readily undergo nucleophilic addition to the CN triple bond[36]. Reaction in this way with Grignard reagents leads to amidines[36]. The addition of acyl chlorides yields *N*-acylchloroformamidines[17,40].



X = O, S, NR^2

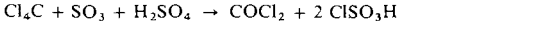


B. Compounds Having Two Formally Similar Ligands on the Carbon Atom

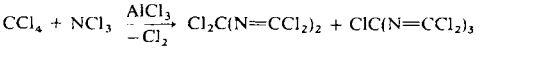
	I $=CCl_2$	II. $=C=O$	III $=C=S$	IV $=C=NR$
1	$Cl_2C=$	$Cl_2C=CCl_2$		
2	O=	$O=CCl_2$	$O=C=O$	
3	S=	$S=CCl_2$	$S=C=O$	$S=C=S$
4	RN=	$RN=CCl_2$	$RN=C=O$	$RN=C=S$	$RN=C=NR$

B 11. Tetrachloromethane (Carbon Tetrachloride)

Though tetrachloromethane can be obtained by perchlorination of carbon disulfide (B III3), it can be included only formally in carbonic acid chemistry as the "tetrachloride of orthocarbonic acid". Substitution of the chlorine atoms in this compound generally calls for extreme conditions. However, tetrachloromethane can be converted into phosgene in the laboratory in oleum at about 80 °C[41].



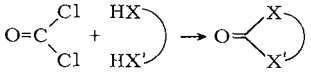
Alcoholysis with sodium alkoxides yields orthoformates and orthocarbonates[42], whereas sulfidizing leads back to carbon disulfide. With nitrogen trichloride or *N*-chloroisocyanide dichloride in the presence of Lewis acids, carbon tetrachloride can form dichloromethane bis(isocyanide dichloride) and chloromethane tris(isocyanide dichloride)[43,64].



B 12. Carbonic Acid Dichloride (Phosgene)[140]

The industrial synthesis of phosgene is based on the addition of chlorine to carbon monoxide in the presence of active charcoal[44].

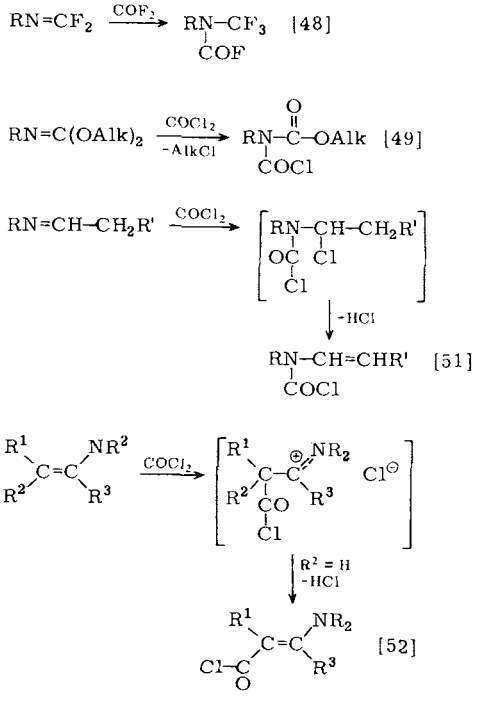
The reactions of phosgene extend mainly to nucleophilic substitutions of the two chlorine atoms, the reactivity being stepped in such a way that monosubstitution products such as carbonic ester chlorides (C II1), thiocarbonic *S*-ester chlorides (C II2), or carbamoyl chlorides (C II4) can be easily prepared. Corresponding reactions with substitution of both chlorine atoms lead *e.g.* to diesters of carbonic acid, thioesters of carbonic acid, ureas, and urethanes. Isocyanates (B II4) can be obtained with primary amines. With suitable bifunctional nucleophiles, phosgene gives a wide range of five-membered and six-membered heterocycles[45].



X, X' = O, S, NR

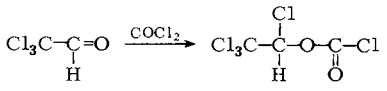
Under Friedel-Crafts conditions, phosgene reacts with aromatic hydrocarbons, dialkylaminobenzenes, *etc.*, to form ketones or carbonyl chlorides, depending on the proportions of the reactants[46].

Phosgene can add to CN multiple bond systems and enamines to form a wide range of compounds, which may be stabilized by formation of secondary products. Mention should also be made of an addition of carbonic acid difluoride.



Phosgene also behaves as an acid chloride toward the carbonic acid derivatives with CN multiple bonds that are described in this article, such as cyanates, cyanogen chloride, isocyanates, and carbodiimides[17,6,47,50,62].

Phosgene can also add to activated carbonyl compounds, such as chloral, in the presence of a tertiary amine[53].



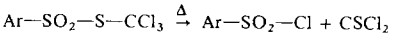
The importance of phosgene as a chlorinating agent will be mentioned here only in passing. Thus phosgene reacts *e.g.* with *N,N*-disubstituted carboxamides to form α,α-dichloroamines ("amide chlorides"), and with ureas to form dichloromethylenediamines ("carbamide chlorides")[53a].

B I3. Thiocarbonic Acid Dichloride (Thiophosgene)

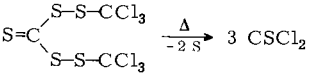
Thiophosgene is obtained by reductive dechlorination of trichloromethanesulfenyl chloride (C I3) or its derivatives.

Trichloromethanesulfenyl chloride itself can be converted into thiophosgene with tin(II) chloride in hydrochloric acid solution[54], with tetralin in organic solution[55], with SO_2[56], or with H_2S[57].

The *S*-trichloromethyl arenethiosulfonates, which are obtainable from aromatic sulfinic acids and trichloromethanesulfenyl chloride, are thermally decomposed into thiophosgene and aromatic sulfonyl chlorides[58].

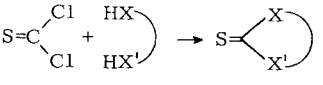


The product formed from sodium trithiocarbonate and trichloromethanesulfenyl chloride decomposes similarly when heated, with elimination of sulfur[59].



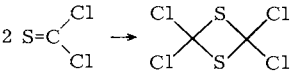
The two chlorine atoms can also be selectively substituted in thiophosgene. If only the first chlorine is replaced by a nucleophilic group, one obtains *e.g.* thiocarbonic *O*-ester chlorides (C III1), dithiocarbonic ester chlorides (C III2), or thiocarbamoyl chlorides (C III4). Replacement of both chlorine atoms then gives symmetrical or unsymmetrical mono-, di-, and trithiocarbonic esters, thioureas, thiourethanes, dithiourethanes, and isothioureas. Isothiocyanates (B III4) are also formed with primary amines, depending on the procedure.

Finally, reaction with suitable bifunctional partners again leads to five-membered or six-membered heterocycles.

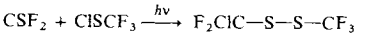


X, X' = O, S, NR

Additions to the CS double bond in thiophosgene are possible, whereas the CO double bond of phosgene cannot undergo such additions. Under the action of sunlight, thiophosgene slowly dimerizes to tetrachloro-1,3-dithietane[60].



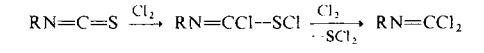
Perhalogenated methanesulfenyl chlorides add smoothly to the thiocarbonyl group of thiocarbonic difluoride in the presence of UV radiation to form disulfides[61].



Like phosgene, thiophosgene also adds to the CN double bond of carbodiimides[62].

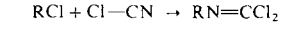
B I4. Iminocarbonic Dichlorides (Isocyanide Dichlorides)

Isocyanide dichlorides can be synthesized by numerous routes[32]. One that is widely applicable is the chlorination of isothiocyanates, which has the desired result in the aliphatic, cycloaliphatic and acylated series, and partly also in the aromatic series, and involves iminochloromethanesulfenyl chlorides (C IV3) as intermediates[32].

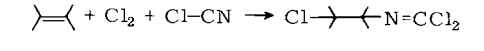


The addition of chlorine to isocyanides proceeds smoothly in many cases[63], whereas the chlorination of isocyanates with phosphorus pentachloride leads to the desired products only in the aliphatic and cycloaliphatic series[32].

The addition of cyanogen chloride to compounds containing reactive chlorine has been extensively studied. It extends from addition to elementary chlorine[4] *via* phosgene[6]

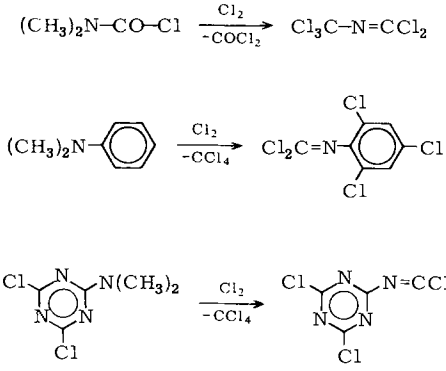


and tetrachloromethane (in the form of *N*-chloroisocyanide dichloride)[64] to acyl and sulfenyl chlorides[7, 8]. A variant of this method is based on the combined action of chlorine and cyanogen chloride on olefins, and leads to 2-chloroalkyl 1-isocyanide dichlorides[5].

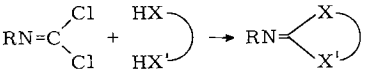


Highly chlorinated aliphatic, aromatic, or heterocyclic isocyanide dichlorides are obtained from *N,N*-dimethylamines in high temperature chlorinations with elimination of acyl chloride or of polychloromethane. Some examples are given below[65].

The number of products that can be formed from isocyanide dichlorides by replacement of one or both of the chlorine atoms is immense (see C IV1, C IV2, C IV4, B II4, B III4, B IV4)[66]. Finally, with strong reducing agents such as trialkylphosphanes, isocyanide dichlorides lose both chlorine atoms to from isocyanides[66].

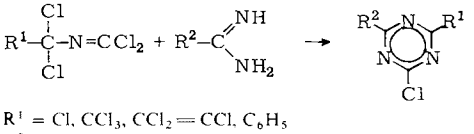


A wide variety of five-membered, six-membered, and higher heterocycles can be obtained by replacement of both chlorine atoms with bifunctional nucleophiles[66].



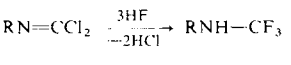
R = alkyl, cycloalkyl, aryl, acyl, RS, RSO_2, $(RO)_2P(O)$;
X,X' = O, S, NR

α-Chlorinated isocyanide dichlorides (*e.g.* trichloromethyl, α,α-dichlorobenzyl, or chlorocarbonyl isocyanide dichloride) exhibit preferential replacement of the α-chlorine atom and one of the chlorine atoms on the carbonic acid C atom with bifunctional compounds to form heterocycles containing chlorine[67].

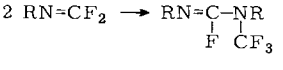


R^1 = Cl, CCl_3, $CCl_2=CCl$, C_6H_5
R^2 = H, alkyl, aryl, CH_3S

The addition reaction of isocyanide dichlorides that has been most extensively studied so far is the reaction with hydrogen fluoride, which leads by chlorine-fluorine exchange to *N*-trifluoromethylamines[66].



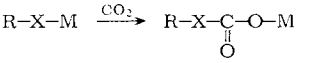
The *N*-trifluoromethylcarbamoyl fluorides, which can be obtained from isocyanide difluorides and carbonyl difluoride, were mentioned in Section B I2. In this connection, mention should be made of the dimerization of isocyanide difluorides to form *N*-trifluoromethylfluoroformamidines[66].



Additions have also been carried out with diazomethane, epoxides, and sodium azide, as well as other compounds[66].

B II2. Carbon Dioxide

As an "inorganic representative" of carbonic acid chemistry, carbon dioxide is distinguished in its reactive behavior only by addition reactions. Thus carbon dioxide is added by alkoxide solutions to form half esters of carbonic acid[68], by ammonia and amines to form salts of carbamic acid[69], and by organometallic compounds to form carboxylic acids[70].

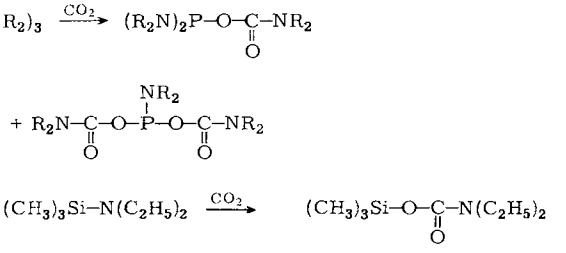


X = O, NR, CR_2; M = metal, H (amine)

A special variant of the formation of carboxylic acids is the Kolbe-Schmidt synthesis of salicylic acid, in which sodium phenoxide is converted into 2- and 4-hydroxybenzoic acids by reaction with carbon dioxide at high temperatures, probably *via* sodium phenyl carbonate[71].

Aromatic hydrocarbons react with carbon dioxide under Friedel-Crafts conditions to give aromatic carboxylic acids[71].

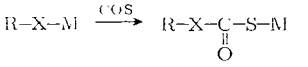
Insertions have been reported for the action of carbon dioxide on amides of trivalent phosphorus or arsenic and on silylamines[72].



B II3. Carbon Oxide Sulfide[73]

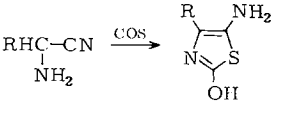
Carbon oxide sulfide, which can be prepared from ammonium thiocyanate and acids[74], is obtained on the industrial scale on decomposition of cellulose xanthate.

Carbon oxide sulfide, like carbon dioxide, can add to alkoxides[75], amines[76], and Grignard compounds[77], with formation of potassium *O*-alkyl thiocarbonate (Bender's salt) and amine salts of thiocarbamic acids or thiocarbonic acids.



X = O, NR, CR_2; M = metal, H (amine)

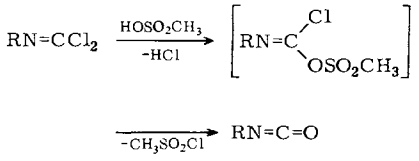
Aliphatic α-amino nitriles undergo addition and cyclization with carbon oxide sulfide to form 5-amino-2-hydroxythiazoles[78].



B II4. Isocyanates[139]

The most important industrial process for the synthesis of monoisocyanates and diisocyanates is based on the phosgenation of primary amines, which can be used both as the free bases and in the form of the hydrochlorides[79]. The lower aliphatic isocyanates, whose boiling points are so close to the decomposition points of the corresponding carbamoyl chlorides that they cannot be separated by distillation, can be obtained in the pure state by thermal cleavage of urethanes[80] or of trisubstituted ureas[81].

Other processes for the production of isocyanates are the Lossen degradation of carboxylic acid azides[82], alkylation of alkali metal or silver cyanate[83], chlorination of monosubstituted aliphatic formamides[84], and the selective reaction of isocyanide dichlorides with methanesulfonic acid, which leads to elimination of methanesulfonyl chloride and formation of isocyanates[85].



Acyl isocyanates are obtained from carbonyl chlorides and silver cyanate, while sulfonyl isocyanates are obtainable by phosgenation of sulfonamides[86].

Isocyanates are practically unique among chemical compounds in their excellent addition capacity, of which industrial use is made in many instances. They can add on all compounds containing mobile protons, possibly in the presence of catalysts, to give stable products in most cases (*e.g.* HF, HCN, hydrogen sulfite, hydroxylamine, hydroxy compounds, thiols, amines, hydrazines, oximes, carboxylic acids, carboxamides, sulfonamides, CH acids)[87].

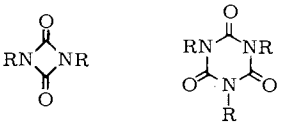
Electrophiles can also add to isocyanates. Bis(chlorocarbonyl)amines are formed on addition of phosgene (cf. B I2). Sulfur dichloride[88], carboxylic acid chlorides[89], and carbamic acid chlorides[90] also add to aliphatic isocyanates in a similar manner.

Isocyanates react with double bond systems, often with 1,2 cycloaddition. However, the resulting four-membered heterocycles decompose readily in most cases with decarboxylation. Thus isocyanates react with carbonyl compounds to form Schiff bases, with *N*-substituted amides to form amidines, with anhydrides of dicarboxylic acids to form imides, with nitroso compounds to form azo compounds, and with sulfoxides to form sulfimides. Addition to semipolar bonds of organophosphorus compounds proceeds particularly readily, and leads in the case of phosphorimides to carbodiimides. This is the basis of the synthesis of carbodiimides from isocyanates with catalysis by phospholene oxides (B IV 4). Olefins give stable β-lactams only with the very reactive chlorosulfonyl isocyanate, and vinyl ethers only with sulfonyl isocyanates, whereas enamines, which have no hydrogen in the β position, can also react with aliphatic and aromatic isocyanates to give four-membered heterocycles. Finally, 1,2-cycloadducts of isocyanates and carbodiimides have also been reported[91].

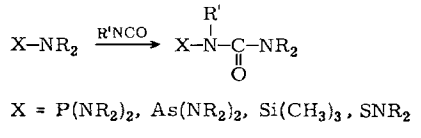
Isocyanates react in 1,3-dipolar additions with their CN double bond as the dipolarophile, *e.g.* with nitrones, azomethine imines, nitrile imines, alkylene oxides, and alkylene carbonates.

Acyl isocyanates with a carbonyl, thiocarbonyl, or imidoyl grouping can also be used to a limited extent as dienes or dienophiles for 1,4 cycloadditions. Other isocyanates can also undergo this reaction in some cases[91].

An important characteristic of isocyanates is the readiness with which they oligomerize. Depending on the reaction conditions, one obtains the dimeric uretdiones, which can be converted back into the monomer by thermal cleavage, or the stable isocyanurates[91].



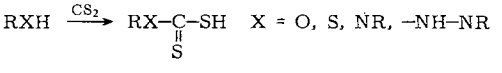
Isocyanates also undergo insertion with amides of trivalent phosphorus or arsenic and with trimethylsilylamines and sulfenamides[72] (cf. B II2).



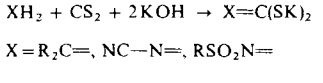
B III3. Carbon Disulfide

Carbon disulfide, a common solvent, is already being used industrially for addition reactions.

In analogy with the reactions of carbon dioxide and carbon oxide sulfide, carbon disulfide adds to alkoxides to form xanthates[92], to thiolates to form esters of trithiocarbonic acid[93], to ammonia and amines to form dithiocarbamic acids[94], and to hydrazines to form dithiocarbazic acids[95].



Carbon disulfide reacts with CH acids[96], cyanamide[97], and primary sulfonamides[98] in alkaline media to give the dialkali metal salts of dithio acids.



Carbon disulfide can also undergo insertions into compounds of trivalent phosphorus[72].

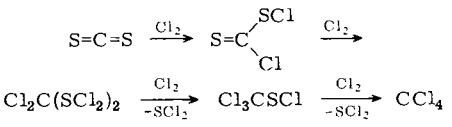
Stable 1,2 cycloadducts are obtained from carbon disulfide only in the presence of sulfur, whereas trithiones are formed with enamines, ketimines, and malodinitrile[99].

Carbon disulfide reacts with hydrazoic acid, nitrile imines, azomethine imines, and alkylene oxides or sulfides to form 1,3 cycloadducts[99].

Unlike the carbonic acid derivatives containing a CN multiple bond, which enter into diene reactions only in excep-

tional cases, carbon disulfide adds to enamines or dienamines in the manner of a Diels-Alder reaction to form α-dithiopyrones[99].

The reaction of carbon disulfide with chlorine leads by addition and subsequent chlorination *via* dichloromethanedi(sulfenyl chloride)[100] and trichloromethanesulfenyl chloride (C I3) to tetrachloromethane (B I1).



B III4. Isothiocyanates

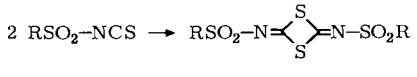
The isothiocyanates, which are isomeric with the thiocyanates (A I3), are characterized as S analogs of the isocyanates (B II4) by the readiness with which they add to nucleophilic and electrophilic systems. They also resemble the isocyanates in their synthesis, as is shown by the thiophosgenation of primary amines or their hydrochlorides[101]. The alkylation of salts of thiocyanic acid and the rearrangement of esters of thiocyanic acid are also analogous to reactions that are commonly used for the synthesis of isocyanates[101]. Other methods for the preparation of isothiocyanates are the oxidation of *N*-monosubstituted dithiocarbamic acids (*e.g.* with heavy metal salts, iodine, phosgene, NaOCl)[101], the cleavage of diarylthioureas with acids[101], and the reaction of isocyanide dichlorides with Na_2S or P_2S_5[38]. Acyl isothiocyanates can be prepared from the acyl chlorides with alkali metal thiocyanates, and in the homogeneous phase with trimethylsilyl isothiocyanate[102]. Finally, sulfonyl isothiocyanates can be synthesized by phosgenation of salts of *N*-sulfonyliminodithiocarbonic acid[103].

The readiness of the aliphatic and aromatic isothiocyanates to undergo addition is less than that of the isocyanates. Thus isothiocyanates are not hydrolyzed in cold water. However, they add other nucleophiles, including CH acids.

$$RN{=}C{=}S + HXR' \rightarrow RNH{-}CS{-}XR'$$
$$X = O, S, NR, CR_2$$

The addition of chlorine to form iminochloromethanesulfenyl chlorides (C IV3) will not be discussed here.

The tendency to oligomerize is also much weaker than in the case of the isocyanates. However, trimers of the isothiocyanates have been reported[104]. The sulfonyl isothiocyanates, like thiophosgene, very readily form dimers, but these can be converted back into the monomers by thermal cleavage[103].



Stable 1,2 cycloadducts can be formed with carbodiimides.

In 1,3-dipolar additions, isothiocyanates can react both with their CN double bond (in reactions with nitrones and azomethine imines) and with their CS double bond (in reactions with diazo compounds and alkylene oxides)[105].

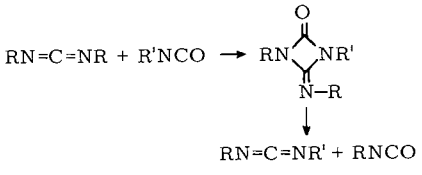
Unlike the sulfonyl isothiocyanates, 2-pyridyl isothiocyanate and imidoyl isothiocyanates dimerize to form six-membered 1,4 cycloadducts[105].

B IV 4. Carbodiimides[106]

Carbodiimides are the tautomers of the cyanamides (A I5) and, like these, they can be prepared by elimination of hydrogen sulfide or of thiol from suitably substituted thioureas or isothioureas[106]. Carbodiimides are also obtainable directly from cyanamides by special alkylation[107], silylation[108], or sulfenylation[109]. A very important method for the synthesis of symmetrical carbodiimides is the catalytically initiated decarboxylation of two molecules of an isocyanate, the catalysts used being oxides or sulfides of phospholenes or phospholanes[110].

$$2RN{=}C{=}O \xrightarrow{-CO_2} RN{=}C{=}NR$$

In the case of sterically hindered aromatic isocyanates, a tertiary amine is sufficient to bring about the decarboxylation[111]. Unsymmetrical carbodiimides can be formed from the resulting symmetrical carbodiimides by the action of other isocyanates *via* thermally unstable uretone imines[111].



Carbodiimides and *N*-sulfonylcarbodiimides can be obtained by "iminophosgenation" of hydrochlorides of primary amines with isocyanide dichlorides[66].

$$RN{=}CCl_2 + R'{-}NH_3^{\oplus}Cl^{\ominus} \rightarrow RN{=}C{=}NR' + 3HCl$$

Other methods for the synthesis of carbodiimides are based *e.g.* on the dehydration of ureas[106], the deamination of guanidines[66], and the pyrolysis of tetrazoles[106].

The reaction of the carbodiimides are dominated by the additions of compounds containing protons (water, hydrogen sulfide, hydrogen cyanide, alcohols, thiols, phenols, amines, carboxylic acids, CH acids *etc.*). The adducts with bifunctional compounds often react with cyclization[106].

$$RN{=}C{=}NR \xrightarrow{HXR'} RN{=}C(XR'){-}NHR$$

Electrophiles such as dicarboxylic acid anhydrides or acyl chlorides also add to carbodiimides[62]. Carbodiimides

X = Cl, RCOO

form heterocyclic products with bifunctional compounds such as oxalyl chloride[112] or diketenes[113].

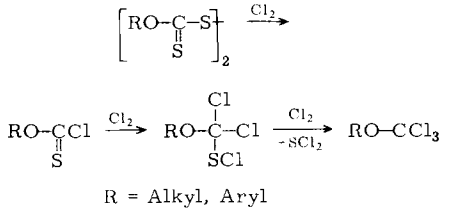
As well as for the above-mentioned synthesis of unsymmetrical carbodiimides, which proceeds *via* a 1,2 cycloadduct, carbodiimides can also be used as dipolarophiles for 1,3 cycloadditions with hydrazoic acid, nitrile imines, diazomethane, and alkylene oxides[114].

C. Compounds with a Chlorine Atom and a Doubly Bonded Ligand or Two Additional Chlorine Atoms

	I	II	III	IV
1	RO—	RO—	RO—	RO—
2	RS—	RS—	RS—	RS—
3	ClS—	ClS—	ClS—	ClS—
4	R_2N—	R_2N—	R_2N—	R_2N—

C I1. Trichloromethyl Ethers

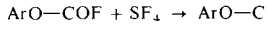
The trichloromethyl ethers and the trichloromethyl thioethers (C I2), like tetrachloromethane, occupy a special place in this discussion, since they cannot be regarded as carbonic acid derivatives in the usual sense. Trichloromethyl ethers can be obtained from *O*-ester chlorides of thiocarbonic acid or from xanthogen disulfides by chlorination at low temperatures. The alkoxy- or aryloxydichloromethanesulfenyl chlorides that occur as intermediates can be isolated[115,116].



R = Alkyl, Aryl

Trichloromethyl ethers react with water, sodium phenoxide, alcohols, and carboxylic acids to form true derivatives of carbonic acid; for example, the reaction with water leads to ester chlorides of carbonic acid, and the reactions with alcohols lead to carbonates[115].

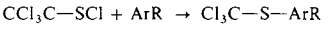
The very stable trifluoromethyl ethers can be obtained from ester fluorides of carbonic acid and sulfur tetrafluoride[117].



C I2. Trichloromethyl Thioethers

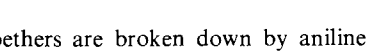
Trichloromethyl thioethers RS—CCl_3 can be obtained by the same synthesis principle as was used for trichloromethyl ethers (C I1), *i.e.* by chlorination of ester chlorides of dithiocarbonic acid in the cold[118].

Aromatic trichloromethyl thioethers can also be synthesized by electrophilic substitution of trichloromethanesulfenyl chlorides (C I3) with aromatic hydrocarbons, phenols, and aromatic amines[119].

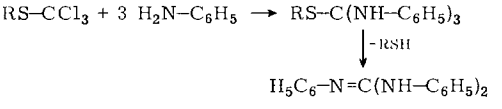


R = H, OH, NR'_2

2-Chlorinated trichloromethyl thioethers can be prepared by addition of trichloromethanesulfenyl chloride to olefins[120].



Trichloromethyl thioethers are broken down by aniline to form triphenylguanidine and the thiol[121].

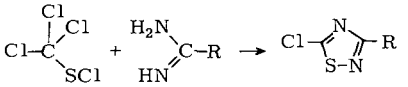


C I3. Trichloromethanesulfenyl Chloride

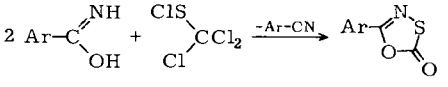
The only synthesis of trichloromethanesulfenyl chloride, which can also be carried out industrially, is based on the iodine-catalyzed chlorination of carbon disulfide (B III3)[120,122]. The relationship of trichloromethanesulfenyl chloride with thiophosgene was reported in Section B I3.

Because of its sulfenyl chloride function, trichloromethanesulfenyl chloride can add to CC and CN multiple bonds[123]. Very extensive studies have been carried out on the substitutions with nucleophiles, in which the chlorosulfenyl grouping reacts preferentially[119,120], though under the action of strong nucleophiles in excess, several or even all of the chlorine atoms can also be substituted, *e.g.* with alcohols to form orthocarbonates or with strongly basic amines to form guanidines[119].

With suitable bifunctional compounds, a smooth ring closure occurs with formation of five-membered heterocycles. Thus amidines and *S*-alkylisothioureas yield 5-chloro-1,2,4-thiadiazoles[119].

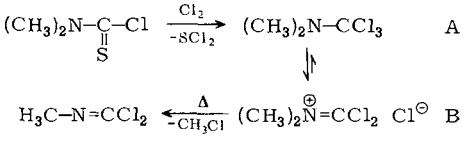


The reaction with aromatic carboxamides leads, with formation of the aromatic nitrile, to 2-oxo-5-aryl-1,3,4-oxathiazoles[119].

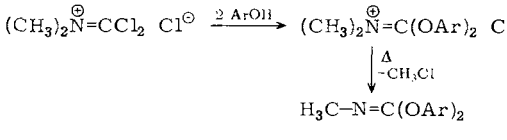


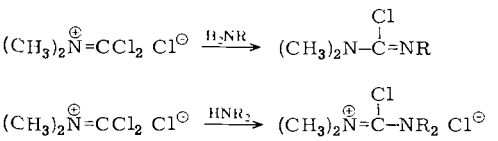
C 14. Dichloromethylenedimethylammonium Chloride (Trichloromethyldimethylamine)

The product, which can be obtained by chlorination of *N*,*N*-dimethylthiocarbamoyl chloride (C III4), is not in the form A with three covalently bonded chlorine atoms, but occurs as the salt-like dichloromethylenedimethylammonium chloride (B)[118,124]. This very reactive compound can be converted by pyrolysis into methyl isocyanide dichloride with elimination of methyl chloride[124].

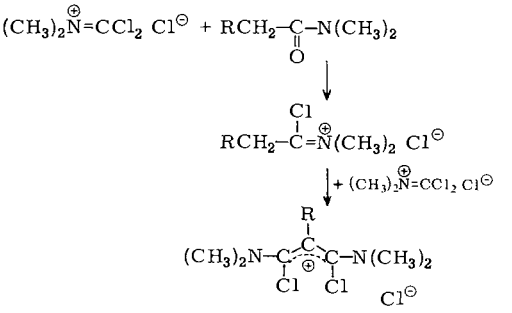


Dichloromethylenedimethylammonium chloride reacts in various ways with nucleophiles. Phenols give novel immonium salts, which form iminocarbonates when heated or are converted into diphenyl carbonates by hydrolysis[124]. With ammonia, all the chlorine atoms are substituted simultaneously with formation of dimethylcyanamide, whereas chloroformamidines (C IV4) or their hydrochlorides ("urea dichlorides") are formed with primary or secondary amines, depending on their basicity[124].



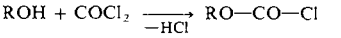


Dichloromethylenedimethylammonium chloride also reacts with active methylene compounds under mild conditions[125]. Thus reaction with *N*,*N*-dimethylcarboxamides in a molar ratio of 2:1 yield novel 1,3-dichloromalonylamines, which can be used for cyclizations[126].



C III. Carbonic Ester Chlorides (Chlorocarbonates)[127]

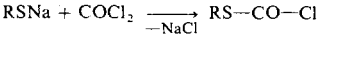
Carbonic ester chlorides are synthesized from phosgene and alcohols or phenols. Primary and secondary alcohols react even without the addition of an HCl acceptor, whereas addition of a base is necessary in the case of tertiary alcohols and phenols.



Carbonic ester chlorides are comparable to the chlorides of carboxylic acids, and react with all nucleophiles including CH acids.

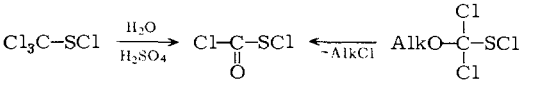
C II2. Thiocarbonic *S*-Ester Chlorides[128]

The thiocarbonic *S*-ester chlorides are obtainable in the same way as the sulfur-free analogs (C III) from phosgene and thiolates. The chlorine in these compounds can again be easily substituted by nucleophilic residues.

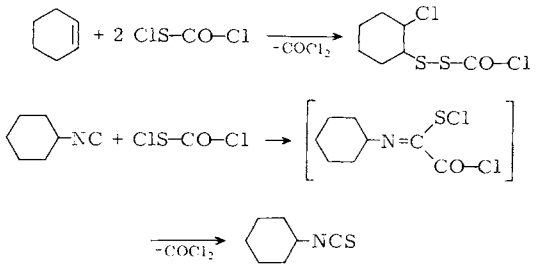


C II3. Chlorocarbonylsulfenyl Chloride[131]

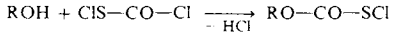
Chlorocarbonylsulfenyl chloride can be prepared by partial hydrolysis of trichloromethanesulfenyl chloride (C I3) in sulfuric acid solution[129] or by thermolysis of alkoxydichloromethanesulfenyl chloride with elimination of alkyl chloride[130].



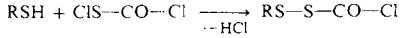
Like the other compounds of the C II series, chlorocarbonylsulfenyl chloride can generally take part only in substitution reactions, and in this case use can be made of the difference in the reactivities of the two chlorine atoms. The sulfenyl chloride function also allows additions, but these frequently proceed anomalously with elimination of phosgene, as shown by the two examples[131].



Chlorocarbonylsulfenyl chloride reacts with alcohols in a molar ratio of 1:1 to form alkoxycarbonylsulfenyl chlorides[131], whereas thiols give the thermodynamically

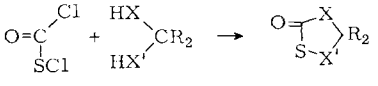


favored disulfide grouping, with formation of alkylchlorocarbonyl disulfides[131].



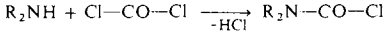
As expected, chlorocarbonylsulfenyl chloride and the alkoxycarbonylsulfenyl chlorides and alkyl chlorocarbonyl disulfides obtainable from it can also react with other nucleophiles.

Chlorocarbonylsulfenyl chloride is also very useful for the synthesis of heterocyclic systems. Thus five-membered rings are obtained, usually in a smooth reaction, with 1,3-bifunctional nucleophiles[131].



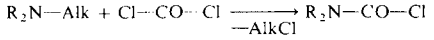
C II4. Carbamoyl Chlorides[132]

Whereas unsubstituted carbamoyl chloride ("urea chloride") and the monosubstituted carbamoyl chlorides that occur as intermediates in the isocyanate synthesis are relatively unstable, the disubstituted carbamoyl chlorides obtainable from secondary amines and phosgene are stable compounds that can be purified by distillation or crystallization.



These compounds are synthesized either in the cold in the presence of a tertiary amine as an acid acceptor or with heating to drive off the hydrogen chloride formed in the reaction.

Tertiary amines with lower alkyl groups can also be converted into carbamoyl chlorides in a sort of Braun degradation with elimination of alkyl chloride



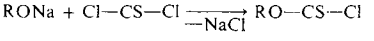
Carbamoyl chlorides are also obtainable by chlorination of dialkylformamides with sulfuryl chloride[124] or sulfur dichloride/pyridine[133].

The carbamoyl chlorides behave toward nucleophiles as acyl chlorides, but with reduced activity. Within this class of compounds, the reactivity decreases still further on transition from the aliphatic to the aromatic members.

Carbamoyl chlorides are also suitable for the synthesis of carboxamides under Friedel-Crafts conditions. In the presence of catalysts such as tin tetrachloride, carbamoyl chlorides add to aliphatic isocyanates to give persubstituted allophanoyl chlorides[90].

C III1. Thiocarbonic *O*-Ester Chlorides[134]

In analogy with the preparation of carbonic ester chlorides (C III), thiocarbonic *O*-ester chlorides can be obtained from thiophosgene if alkoxides or phenoxides are used.



Besides the nucleophilic substitutions, additions of chlorine to the CS double bond have been reported; as was mentioned in Section C II, these reactions lead to alkoxy- or aryloxydichloromethanesulfenyl chlorides and then to trichloromethyl ethers.

C III2. Dithiocarbonic Ester Chlorides[128]

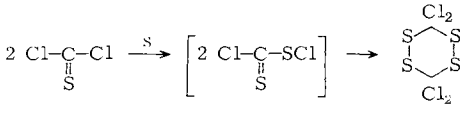
The dithiocarbonic ester chlorides are obtainable from thiols or thiolates and thiophosgene; trithiocarbonic diesters or dithiocarbamic esters, for example, can be obtained from these in normal substitution reactions.

The addition of chlorine to the CS double bond leads here *via* the alkylthiodichloromethanesulfenyl chloride to the trichloromethyl thioether (cf. Section C I2).

C III3. Chlorothiocarbonylsulfenyl Chloride

Chlorothiocarbonylsulfenyl chloride is the only one of the carbonic acid derivatives discussed here that has not yet been synthesized.

The sulfurization of thiophosgene, which was described in 1887[135], leads not to this product but to a dimer, as our experiments have shown. The formation of a 1,2,4,5-tetrathiane may be assumed on the basis of mass-spectroscopic studies.



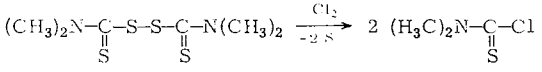
The structure is confirmed by the mass-spectroscopically detected fragmentation to tetrachloroethylene. The formation of the heterocycle becomes understandable if one considers that sulfenyl chlorides add to CS double bonds[123].

C III4. Thiocarbamoyl Chlorides[136]

As in the case of the carbamoyl chlorides, only the disubstituted compounds are stable among the thio analogs. They can be synthesized by thiophosgenation of secondary amines, which may be used in the form of their hydrochlorides, as in the phosgenation.

$$R_2NH + Cl{-}CS{-}Cl \rightarrow R_2N{-}CS{-}Cl$$

The chlorinative cleavage of tetrasubstituted thiuram disulfides with simultaneous removal of sulfur also leads directly to thiocarbamoyl chlorides.



Finally, thiocarbamoyl chlorides are also obtained on chlorination of disubstituted thioformamides with sulfur dichloride/pyridine or chlorine[133, 137].

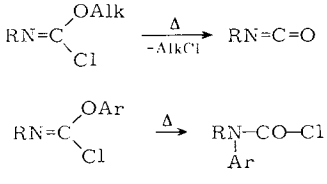
The thiocarbamoyl chlorides are comparable to the carbamoyl chlorides in their reactivity in nucleophilic substitutions. The dichloromethylenammonium chlorides (C I4) are formed on chlorination.

C IV1. Iminocarbonic Ester Chlorides[38]

The iminocarbonic ester chlorides, which are readily obtainable from isocyanide dichlorides (B I4) and alkoxides or phenoxides, contain a mobile chlorine atom, which can be used for further substitutions.

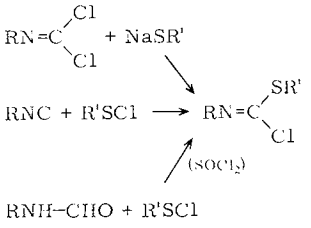
$$RN{=}CCl_2 + NaOR \rightarrow RN{=}C(Cl){-}OR$$

The *O*-alkyl esters of this class of compounds readily lose alkyl chloride when heated, with formation of isocyanate, whereas the *O*-aryl esters isomerize to carbamoyl chlorides in the manner of a Chapman rearrangement.



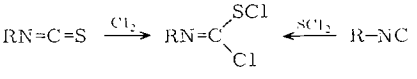
C IV2. Iminothiocarbonic Ester Chlorides[38]

There are three fundamental routes for the synthesis of this class of compounds: the reaction of isocyanide dichlorides with thiolates in a molar ratio of 1:1, the addition of sulfenyl chlorides to isocyanides, and the addition of sulfenyl chlorides to monosubstituted formamides in the presence of thionyl chloride. The chlorine atom in these compounds can again be substituted by nucleophilic residues.

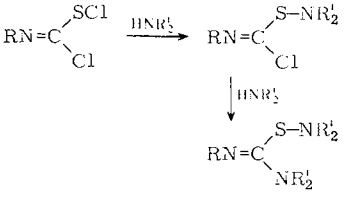


C IV3. Iminochloromethanesulfenyl Chlorides[131]

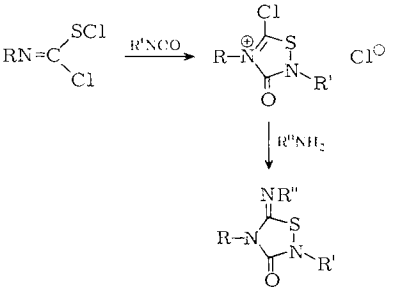
Iminochloromethanesulfenyl chlorides are readily obtainable by addition of chlorine to isothiocyanates or by addition of sulfur dichloride to isocyanides.



According to the investigations carried out so far, iminochloromethanesulfenyl chlorides give the expected substitution products only with amines.

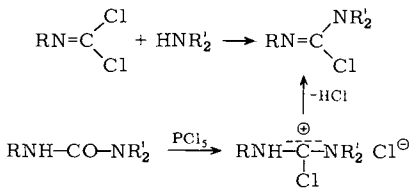


On the other hand, iminochloromethanesulfenyl chlorides are very suitable for cyclizations, in which use is made of the readiness with which the sulfenyl chloride group adds to CC and CN multiple bonds. In the resulting salts containing a five-membered heterocyclic cation, the chlorine atoms may be substituted by nucleophiles in a secondary reaction. This is illustrated by the addition of isocyanates. In addition to isocyanates, other classes of compounds that react particularly readily are isothiocyanates and cyanates, as well as vinyl ethers and enolizable aldehydes and ketones.



C IV4. Chloroformamidines[38]

Chloroformamidines are obtainable by reaction of isocyanide dichlorides (B I4) with primary or secondary amines in a molar ratio of 1:1 or by chlorination of substituted ureas[138], *e.g.* with phosphorus pentachloride.



The alkyl-substituted chloroformamidines are sufficiently basic to add hydrogen chloride with formation of chloroformamidinium chlorides ("urea dichlorides").

In nucleophilic substitutions, an increase in reactivity is observed from purely aliphatic *via* aromatic-aliphatic compounds to *N*-acylated chloroformamidines.

6. Conclusion

It is remarkable that since the first experiments on the synthesis of carbonic acid derivatives by *F. Wöhler* about 150 years ago (1828: synthesis of urea from ammonium thiocyanate) this field of chemistry has only just been revived and enlarged by some new classes of compounds.

It is hoped that the present review on carbonic acid derivatives, which command great interest for both pure and applied organic chemistry, may help to ensure that this class of compounds will in future continue to enrich our theoretical and practical knowledge.

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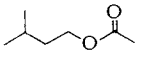
Recent Results in Insect Pheromone Chemistry

By John G. MacConnell and Robert M. Silverstein[*]

Pheromones are substances which are secreted to the outside by an animal, especially an insect, and received by a second individual of the same species, in which they release a specific reaction, for example, a definite behavior or developmental process. The name is derived from the Greek *pherein* (to bear, transmit) and *hormon* (impel, excite). Pheromones include, *inter alia*, sex attractants, warning substances, and "aggregation pheromones". Many of these substances are effective at very low concentration. The insect pheromones are predominantly derivatives of long-chain, slightly branched hydrocarbons.

1. Introduction

Perhaps the first written account of a pheromonal interaction in insects was that of *Charles Butler*, who in 1609 described how honeybees are attracted and provoked to mass attack by a substance released as a result of a single initial sting[1]. *Huber*, in 1792, found that this attack behavior could be attributed to the sting odor[2]. In 1962, more than 350 years after *Butler*'s description, a compound at least partially responsible for the mass attack (the so-called sting pheromone) was identified as *iso*-pentyl acetate *(1)*[3].



(1)

To date, literally hundreds of pheromonal interactions have been demonstrated or implicated in organisms as diverse as rodents[4], coelenterates[5], crabs[6], tadpoles[7], rhesus monkeys[8], fungi[9], algae[10], and earthworms[11]; as might be expected, there has been much speculation about human pheromones[12].

It is our goal in this article to review selectively recent work in the area of insect pheromones, paying particular attention to those of known chemical constitution. To avoid the problems of classification of pheromones of uncertain biological function or significance, or those whose elicited response depends on context, we have organized our review on a taxonomic basis rather than on a chemical class or presumed pheromonal function basis.

Although we are nominally reviewing insect pheromones, we also include recent work on some other arthropods. We exclude from this discussion the already vast literature on insect hormones, except where these substances have been shown to have some role in intraspecific communication. We also exclude what appear to be purely defensive secretions.

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2. Definitions

Karlson and *Butenandt*[13] and *Karlson* and *Lüscher*[14,15], in 1959, proposed the term "pheromone" for "substances which are secreted to the outside by an individual and received by a second individual of the same species, in which they release a specific reaction, for example, a definite behaviour or a developmental process"[14]. Two general classes of pheromones were distinguished[13]: the olfactorily active, and the orally active. These two groups correspond closely to the "releaser-primer" terminology of *Wilson* and *Bossert*[16]. The *releasers* involve a more or less immediate behavioral response usually lasting only a few seconds or minutes once the chemical signal is discontinued; the *primers* involve long-term, physiological changes[16].

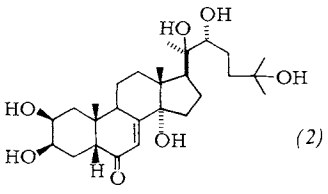
3. Arthropoda Excluding Insecta

The huge phylum Arthropoda is divided into several classes which range from the extinct Trilobita and the obscure Tardigrada and Pentastomida, to the familiar Crustacea (lobsters, barnacles, pill bugs, *etc.*), Arachnida (spiders, scorpions, ticks and their allies), Diplopoda (millipedes), Chilopoda (centipedes), and, of course, Insecta. In the next two Sections, we discuss some of the pheromonal interactions known from arthropods other than insects.

3.1. Crustacea

Sexual attraction in crustaceans of the order Decapoda, which includes lobsters, crabs, shrimps, *etc.*, has been known for some time[17]. Recently it was shown by *Ryan*[6] that water in which premolt females of the crab *Portunus sanguinolentus* have been kept elicits in males of this species the same characteristic response as does the female itself. Noting that in many decapods mating occurs immediately after the female molts, *Kittredge*, *Terry*, and *Takahashi*[18] were led to suspect that the crustacean molting hormone, crustecdysone *(2)*[19], might also be the sex pheromone released by the female. They found that premating behavior was exhibited by males of the crab *Pachygrapsus crassipes* exposed to very dilute solutions of crustecdysone. Indeed, males of *P. crassipes* respond to solutions as dilute as

10^{-13} M. Two crab species in the genus *Cancer* also respond to somewhat higher concentrations of crustecdysone. Although it was not rigorously identified, it appears that the sex pheromone of these crabs is either their own molting hormone, crustecdysone, or some compound very similar to it. Based largely on this finding, *Kittredge* and *Takahashi* recently advanced a proposal on the evolution of sex pheromone communication in the Arthropoda[20].



(2)

The female of the crab *Callinectes sapidus* uses another molting hormone, callinecdysone A, as its only molting hormone during the early premolt stage[21]. Later, as mating approaches, small amounts of crustecdysone accompany the callinecdysone A[21]. It is possible that in this species, unlike *Cancer* and *Pachygrapsus*, two distinct compounds are used for the two activities, the callinecdysone A functioning mainly as the molting hormone and the crustecdysone as the sex pheromone.

Sex pheromonal communication has recently been demonstrated in the amphipod crustacean, *Gammarus duebeni*[22].

3.2. Arachnida

Among the spiders (order Araneae), evidence has recently been obtained for sex pheromones in four species in the family Lycosidae[23].

Among the mites and ticks (order Acari), there is evidence for sex pheromones in at least four species[24, 25, 26]. In *Tetranychus urticae*[25] and *Amblyomma americanum*[26], the males are attracted to the females; in *A. maculatum*, however, the females are attracted to the males[24]. In very recent work, *Berger*[27], working with *A. americanum*, has identified a female-derived sex pheromone as 2,6-dichlorophenol. The phenol is present in mature females in amounts approximating 5 nanograms per animal. Several careful experiments failed to support the hypothesis that the phenol was an artifact. *Berger* has found 2,6-dichlorophenol in similar amounts in Gulf Coast ticks, *A. maculatum*[28]. Experiments are underway to determine whether females can synthesize the phenol from appropriately labeled precursors[28].

4. The Insects

According to *Borror* and *DeLong*[29], the class Insecta contains 27 orders; we consider only those orders in which pheromonal communication is of known primary importance. The various orders are discussed in the sequence and with the limits given by *Borror* and *DeLong*.

4.1. Orthoptera

Both releaser and primer effects have been found in the Orthoptera (roaches, grasshoppers, locusts, *etc.*), but no orthopteran pheromones have been chemically identified.

Probably the best known problem among orthopteran pheromones is that related to the structure of the sex attractant produced by the female American cockroach, *Periplaneta americana* (family Blattidae). This pheromone not only attracts the male, but is also important in sex recognition and in the release of courtship behavior in the male[30]. *Jacobson, Beroza*, and *Yamamoto*[31] proposed the structure 2,2-dimethyl-3-isopropylidenecyclopropyl propionate, for this pheromone, but this proved to be incorrect[32].

Recently, *Bowers* and *Bodenstein*[33] found several plant-derived compounds to be sex pheromone mimics. In addition, on the basis of some chemistry carried out on crude pheromone preparations, they concluded that the natural pheromone may be an unsaturated ketone with additional functionality sensitive to base. The structure remains unknown. For reviews on cockroach mating behavior, see the papers by *Roth* and *Willis*[34] and *Barth*[35].

Several orthopteran species exhibit aggregation behavior at certain times in their lives; aggregation mediated by pheromones has been observed in the cockroach *Blattella germanica*[36], in the cricket *Acheta domestica*[37], and in the locust *Schistocerca gregaria*[38]. In addition to the pheromone responsible for aggregation, *B. germanica* also produces a primer pheromone: young nymphs reared in isolation are delayed in growth and development[39]. Females of *S. gregaria* have a strong tendency to oviposit in groups[38]; in addition, both sexes produce primer pheromones which act to synchronize the production of adults in a very localized population[40]. *Blight et al.*[41] have identified several volatile compounds from laboratory colonies of this locust, but the significance of these substances is unknown.

4.2. Isoptera

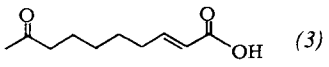
Termites constitute the order Isoptera. Pheromonal communication is well developed among these relatively primitive insects[42].

The most primitive of the termite families, the Mastotermitidae, contains but one species, *Mastotermes darwiniensis*. *Moore* (cited in Ref. [42b], p. 428) has found that extracts of the sternal gland of *M. darwiniensis* will induce trail following in this species.

Lüscher[43] found that workers of *Kalotermes flavicollis* (Kalotermitidae) perceive the presence of the primary reproductives (the "king" and "queen") *via* nonvolatile substances occurring on the reproductives' antennae. If antennal contact is prevented, the workers behave as if the colony had lost its royal pair and will raise a supplementary reproductive pair. *Hrdý et al.*[44] found that extracts of honeybee "queen substance" when fed to queenless workers of *K. flavicollis* largely inhibit the development of supplementary reproductives; extracts of queens of

Odontotermes (family Termitidae) inhibit queen rearing by worker honeybees[45]. The implication is that worker termites may perceive the presence of their queen *via* a pheromone not unlike that used by the honeybee queen, (*E*)-9-oxo-2-decenoic acid *(3)*. A compound which may be identical to queen substance was recently identified in extracts of queen heads of *Odontotermes assmuthi*[46].

An attractant, (*Z*)-3-hexen-1-ol *(4)*, appears to be important in the attraction of *K. flavicollis* to nestmates, particularly to larvae and nymphs[47].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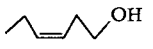
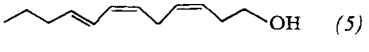

(4)

Hummel and *Karlson*[48,49] have isolated from *Zootermopsis nevadensis* (family Hodotermitidae) several fractions which are active in the trail pheromone bioassay. An active hydrocarbon, $C_{11}H_{20}$, of unknown structure, was isolated as was hexanoic acid, from an extract of termites. Hexanoic acid is reported[50] to have the same biological activity as the natural pheromone. Farnesol (which does not occur in the trail pheromone secretion) is equally active[50], and ethyl dodecanoate is some 200 times as potent as hexanoic acid in eliciting trail following (10^7 Spureinheiten per mg)[51]. *Pasteels*[52] has shown that the sternal glands of adults of both sexes of *Z. nevadensis* produce attractants for the opposite sex. During nymphal stages, this gland produces the trail pheromone[53]; later, in the adult, it secretes a sex-specific attractant.

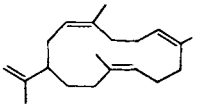
Esenther et al.[54] reported that cultures of the wood-rotting fungus *Lenzites trabea* produce a material which is attractive to *Reticulitermes flavipes* and *R. virginicus* (Rhinotermitidae). *Smythe et al.*[55] found that one of the attractants elicits trail following in the termites and associated the natural trail pheromone with this substance from the fungus-infected wood. Termite extracts were shown to contain the same compound[55]. This substance was isolated[56] and identified[57] as (*Z*,*Z*,*E*)-3,6,8-dodecatrien-1-ol *(5)*.


(5)

Stuart (Ref. [42d], particularly pp. 96—97 and 100—101) has questioned this identification of the *Reticulitermes* trail pheromone; the following discussion more or less summarizes *Stuart*'s arguments. In spite of the extreme activity of synthetic *(5)* in the bioassay[57b], the experiments described so far have not demonstrated unequivocally that this compound is actually secreted by the termites and deposited as the trail-marking pheromone. Since only whole body extracts have been made, there is no proof that the trienol is produced or stored in the sternal gland, the organ presumed to store and deposit the trail pheromone[42c]. In addition, in view of the relatively large amount of the trienol occurring in the surrounding wood[55], it is quite possible that the trienol isolated from the termite extracts does not represent sternal gland contents, but contents of the gut (or any other tissue not associated with trail laying). That the termites are able to follow an artificial trail of an extremely attractive substance may not be unexpected.

Moore[58] has identified several monoterpenes in the defensive secretions of termites from four genera (*Nasutitermes*, *Tumulitermes*, *Amitermes*, and *Drepanotermes*) in the largest termite family, Termitidae. He has also suggested that they may serve as alarm pheromones. This suggestion, however, has been questioned by *Maschwitz*[59] and *Stuart* (Ref. [42d], pp. 91—93).

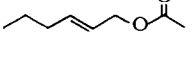
Stuart[53,60] showed that *Nasutitermes* termites mark a trail with a substance deposited from the sternal gland. *Moore* subsequently isolated from extracts of whole *N. exitiosus* termites a trail-active fraction[61]. The molecule was characterized as a diterpene hydrocarbon, $C_{20}H_{32}$, with four double bonds and one ring[61]. On the basis of UV and NMR spectra and of microozonolysis experiments, this substance (nasutene) has been tentatively assigned structure *(6)*[62]. The cembrane skeleton was confirmed by comparison of perhydrocembrene with perhydronasutene, which proved identical. The precise location and stereochemistry of the double bonds are not certain. This substance also elicits trail-following in *N. walkeri* and *N. graveolus*[61]. It remains to be seen if this substance originates in the sternal gland.


(6)

4.3. Hemiptera

The Hemiptera (true bugs) are arranged into about 50 families; evidence for pheromonal communication has been reported in the hemipteran families Cimicidae[63], Lygaeidae[64], Miridae[65], Pyrrhocoridae[66], and Reduviidae[67].

The liquid in the abdominal glands of males of the giant water bug, *Lethocerus indicus* (family Belostomatidae) is used in Thailand as a seasoning for certain foods. *Butenandt* and *Tâm*[68] identified the major volatile constituent as (*E*)-2-hexenyl acetate *(7)*. They postulated that it may serve as a sex attractant or aphrodisiac. *Pattenden* and *Staddon*[69], however, have presented evidence that the ester is neither sex- nor species-specific.


(7)

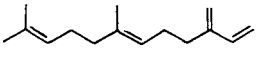
There is evidence that the bronze-orange bug, *Musgraveia* (=*Rhoecocoris*) *sulciventris*, and the southern green stink (or green vegetable) bug, *Nezara viridula* (Pentatomidae), produce pheromones. *Park* and *Sutherland*[70] have proposed that the (*E*)-2-octenyl acetate that they isolated from a steam distillate of both sexes of *M. sulciventris* may act as an attractant or aphrodisiac. The same function

may also be served by the (*E*)-2-decenyl acetate found in the related bug, *Biprorulus bibax*[70]. *Gilby* and *Waterhouse*[71] identified eighteen compounds in the scent secretion of *Nezara viridula*. Although most of these compounds may be used for defensive purposes, a sex pheromone may be among them, for *Mitchell* and *Mau*[72] have shown that males of *N. viridula* produce a substance that is highly attractive to females.

4.4. Homoptera

The order Homoptera includes the cicadas, aphids, scale insects and allies; over 30000 species are known. Chemical communication has been demonstrated in the families Aphididae[73], Coccidae[74], Diaspididae[75], and Pseudococcidae[76].

Kislow and *Edwards*[77] found that the green peach aphid, *Myzus persicae*, (Aphididae) is repelled by its own defensive secretion and by squashed aphids. The substance responsible for this behavior has been designated an alarm pheromone and identified by *Bowers et al.*[78] as (*E*)-β-farnesene *(8)*. It has also been identified in the aphids *Macrosiphum*



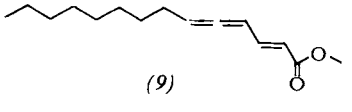
(8)

rosae, *Acyrthosiphon pisum*, *Schizaphis graminum*, and *Aphis gossypii*, where it also presumably acts as an alarm pheromone[78].

4.5. Coleoptera

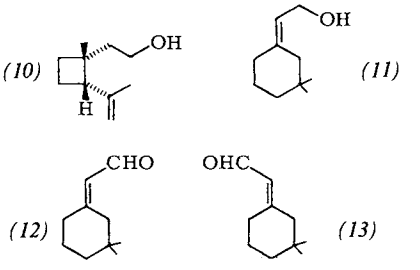
Coleoptera (beetles and weevils) is the largest order of insects and has an appropriately large literature on pheromonal communication. In addition to the families discussed below, pheromones have been suggested or demonstrated in the following families: Anobiidae[79], Buprestidae[80], Carabidae[81], Chrysomelidae[82], Coccinellidae[83], Lampyridae[84], Lycidae[85], Malachiidae[86], Meloidae[87], Platypodidae[88], Staphylinidae[89], and Tenebrionidae[90].

Hope et al.[91] observed that males of the dried bean beetle, *Acanthoscelides obtectus* (Bruchidae) produce a sweet, fruity odor and suggested this might be a pheromone. In 1970, *Horler*[92] identified this substance as (−)-methyl (*E*)-2,4,5-tetradecatrienoate *(9)*, which is the first known allenic sex pheromone. The racemic ester has recently been synthesized[93].



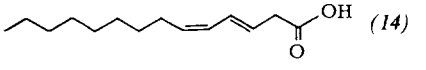
(9)

Males of the boll weevil, *Anthonomus grandis* (Curculionidae), produce a pheromone that attracts the females[94]. A suitable bioassay was developed[95], and *Tumlinson et al.*[96] identified the four synergistic components of the pheromone as (+)-2-(*cis*-isopropenyl-1-methylcyclobutyl)-ethanol *(10)*, (*Z*)-2-(3,3-dimethylcyclohexylidene)ethanol *(11)*, (*Z*)-2-(3,3-dimethylcyclohexylidene)acetaldehyde *(12)*, and (*E*)-2-(3,3-dimethylcyclohexylidene)acetaldehyde *(13)*. Syntheses of the cyclohexane[97] compounds and of the cyclobutane[98] compound have recently been reported. The mixture of the four synthetic compounds is attractive to females in the field[99].



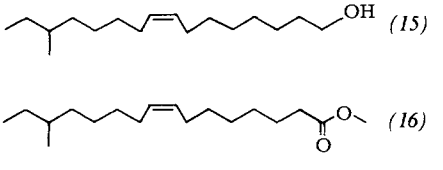
(10) *(11)* *(12)* *(13)*

The sex attractant of the black carpet beetle, *Attagenus megatoma* (Dermestidae), has been identified[100] as (*E,Z*)-3,5-tetradecadienoic acid *(14)*; a synthesis of this acid and its geometric isomers has been reported[101].



(14)

Species in the dermestid genus *Trogoderma* are very important pests of stored grains and consequently have received considerable attention regarding control and eradication. Sex pheromones are present in females of several species[102], and *Yinon* and *Shulov*[103] have presented evidence for an aggregation pheromone in *T. granarium*. The "assembling scent" components of *T. granarium* have been identified[104] as common free fatty acids (oleic, palmitic, and linoleic) and their ethyl esters. Two of the four attractive components of the female *T. inclusum* pheromone were identified by *Rodin et al.*[105] as (*Z*)-(−)-14-methyl-8-hexadecen-1-ol *(15)* and (−)-methyl (*Z*)-14-methyl-8-hexadecenoate *(16)*. *DeGraw* and *Rodin*[106] have published syntheses of these two compounds. Cross attraction studies have been reported for *T. inclusum*, *T. simplex*, *T. variabile*, *T. glabrum*, and *T. sternale*[107a].



(15) *(16)*

The sex attractant pheromone of *T. glabrum* consists of six components, each of which is active individually. Three of these have been identified as hexanoic (caproic) acid, γ-caprolactone, and the (*E*) isomer of compound *(15)*; the others are the next lower and higher homologs of compound *(16)*, and a long chain unsaturated alcohol[107b]. *Lilly* demonstrated[108] that females of the sugar beet wireworm, *Limonius californicus* (Elateridae) produce a sex attractant. It was identified in 1968 by *Jacobson*, *Lilly*,

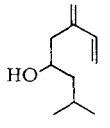
and *Harding*[109] as pentanoic (valeric) acid. A carboxylic acid has also been implicated as the sex pheromone of the Pacific Coast wireworm, *L. canus*[110]. Sex pheromones have also been reported in the elaterid genera *Agriotes*[111], *Ctenicera*[111], and *Hemicrepidius*[112].

The grass grub beetle, *Costelytra zealandica* (family Scarabaeidae), is attracted to certain synthetic resins[113], particularly a phenol-formaldehyde resin. The natural pheromone from females was subsequently isolated and identified as phenol[114]. Apparently the phenol is not produced by the *C. zealandica* females themselves but by bacteria that live in the colleterial glands in their abdomens[115]. It would be interesting to see if virgin females raised under sterile conditions (or treated with appropriate antibiotics) are attractive to males.

The bark beetles in the family Scolytidae have been the subject of extensive pheromone studies because of their economic importance; an estimated annual loss of about 5×10^9 board feet of timber in the USA is attributed to them.

Typically, individuals of one sex select the individual host tree in which mating and oviposition occur. In the process of excavating a "nuptial" chamber, frass (a mixture of wood fragments and fecal pellets) is extruded, whereupon a mass attack by both sexes ensues in response to the pheromones in the frass.

Isolation and identification of the attractant pheromone in the frass of male *Ips paraconfusus* Lanier (= *Ips confusus* LeConte) represents the first identification of an attractant in the order Coleoptera[116]. The attractant pheromone consists of three monoterpene alcohols: (−)-2-methyl-6-methylene-7-octen-4-ol *(17)*, (+)-*cis*-verbenol *(18)*, and (+)-2-methyl-6-methylene-2,7-octadien-4-ol *(19)*. These three compounds have been synthesized[117].



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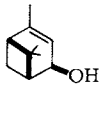

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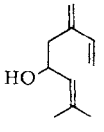

(19)

The first and third compounds were later assigned the trivial names ipsenol and ipsdienol, respectively, since they are widely distributed through the genus *Ips*. None of these compounds is active individually, but the combination of all three attracts beetles in the field. Ipsenol has recently been reported to be the aggregating pheromone for *Ips grandicollis*[118], and ipsdienol plus *cis*-verbenol for *Ips calligraphus*[119]. *trans*-Verbenol *(20)* has been reported in hindguts of male and female *Ips calligraphus*[119], and linalool *(21)* has been identified in frass

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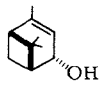
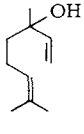
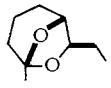




(21)

of female *Ips paraconfusus* and male *Ips pini*[120a]. No biological significance has been attached to either compound, but linalool is of interest in that it is isomeric with ipsenol and can readily be mistaken for it because of very similar gas chromatographic behavior. Cross attraction studies have been carried out on several *Ips* species[120b].

The attractant pheromone of the female Western pine beetle, *Dendroctonus brevicomis*, consists of *exo*- *(22)* and *endo*-7-ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]octane *(23)*, named *exo*-brevicomin and *endo*-brevicomin, respectively[121].



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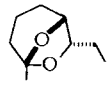


(23)

(24)

The response of both sexes is strongly synergized by myrcene (from the tree resin) and by 1,5-dimethyl-6,8-dioxabicyclo[3.2.1]octane *(24)* (called frontalin[122]) from the male[123]. The three bicyclic ketals have been synthesized[122, 124].

Three large-scale field tests have been conducted in two areas that have been chronically infested with *D. brevicomis*.

A mixture of *exo*-brevicomin, frontalin, and myrcene was used to bait large sticky traps. No definitive statements can be made until much more information has been assimilated, but qualitative, intuitive evaluations look very promising.

The pheromone chemistry and biology of three other bark beetles, *D. frontalis*, *D. ponderosae*, and *D. pseudotsugae*, have also been reported in several papers[*] and some attempts have been made to summarize the arguments involving methodology and interpretation of pheromone studies of bark beetles in general[123a, 125].

4.6. Lepidoptera

In 1965, *Jacobson*[126] listed 140 species of Lepidoptera suspected of producing pheromones; in 1970, he added another 31 species[127]. Most of the identified female sex pheromones are unsaturated normal aliphatic alcohols or acetates (for reviews, see Refs. [127—136]). We shall now focus our attention on some structurally unusual lepidopterous pheromones, on pheromones produced by males, and on some recent structural proposals.

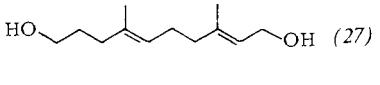
Some species of tiger moths (Arctiidae) in the genera *Holomelina* and *Pyrrharctia* utilize the saturated hydrocarbon 2-methylheptadecane *(25)* as a female sex pheromone[137].

(25)

Males of some butterflies in the family Danaidae seduce their respective females with aphrodisiac scents disse-

[*] The reader is referred to the following works: *J. A. A. Renwick* and *J. P. Vité*, Contrib. Boyce Thompson Inst. Plant Res. *24*, 283 (1970); *J. A. Rudinsky*, *ibid. 24*, 311 (1970); *J. P. Vité* and *J. A. A. Renwick*, *ibid. 24*, 323 (1970); *J. A. A. Renwick*, *ibid. 24*, 337 (1970); *J. P. Vité*, *ibid. 24*, 343 (1970).

minated by brushlike struktures ("hair-pencils") on the abdomen[138]. In the genera examined, *Danaus*[139], *Lycorea*[140], and *Euploea*[139c], several unusual compounds have been identified: 2,3-dihydro-7-methylpyrrolizin-1-one *(26)*[139a,c,d,140], (*E*,*E*)-3,7-dimethyl-2,6-decadiene-1,10-diol *(27)*[139a], and the diacid corresponding to *(27)*[139b].



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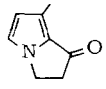

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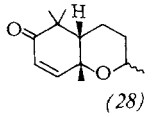
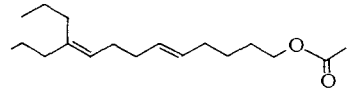


(28)

A second component of the hair-pencil secretion of the monarch butterfly, *Danaus plexippus*, has been isolated and has tentatively been assigned the structure: *cis*-1,3,7,7-tetramethyl-2-oxabicyclo[4.4.0]dec-9-en-8-one *(28)*[140b].

The pink bollworm moth, *Pectinophora gossypiella* (Gelechiidae) uses (*E*)-10-propyl-5,9-tridecadienyl acetate *(29)* as its female sex pheromone[141]; the propyl side chain makes this an unusual natural product. This compound has also been synthesized[142].



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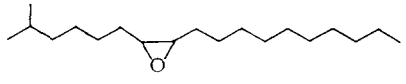

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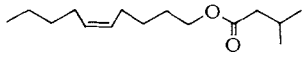
After many years of research, the sex attractant of the female gypsy moth, *Porthetria dispar* (Lymantriidae), has been identified. *Bierl*, *Beroza*, and *Collier*[143] identified the pheromone ("disparlure") as (*Z*)-7,8-epoxy-2-methyloctadecane *(30)*. On the basis of a series of microchemical tests[144], the pheromone was postulated to be an alkyl epoxide. Treatment of the original extract with *m*-chloroperbenzoic acid increased activity tenfold, supporting the epoxide hypothesis and suggesting a search for the precursor olefin[145]. An olefin was isolated that was highly active in the bioassay after epoxidation; it was identified as (*Z*)-2-methyl-7-octadecene. The synthetic pheromone, properly formulated, is at least as attractive to males as are live females[146]; it promises to be useful in the control of the gypsy moth[147]. A synthesis has recently been reported by *Eiter*[148].

Male moths in the family Noctuidae have "hair-pencils" as do the danaids discussed above; their secretions are believed to serve the same purpose[149]. Benzaldehyde has been identified in several species[149a,150], as have several other simple compounds[150a]. In the southern armyworm, *Pseudaletia separata*, it has been suggested[150b] that benzaldehyde serves to inhibit the female's initial escape reaction from the male, although in *P. unipuncta* it would appear that benzaldehyde may not be of communicative significance[150c].

Röller et al.[151] identified *n*-undecanal as the sex attractant of the greater wax moth, *Galleria mellonella* (family Pyralidae). This aldehyde and (*Z*)-11-octadecenal, both produced by males of *Achroia grisella*, have been reported by *Dahm et al.*[152] to be components of the sex pheromone of this pyralid species.

Henderson et al.[153] identified the sex pheromone of the female pine emperor moth, *Nudaurelia cytherea* (Saturniidae), as (*Z*)-5-decenyl 3-methylbutanoate *(31)*.



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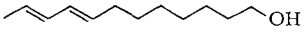
Sex pheromones have been demonstrated in many species in the family Tortricidae[154]; here we consider those of only four species. *Weatherston et al.*[155] identified the sex pheromone in females of the eastern spruce budworm, *Choristoneura fumiferana*, as (*E*)-11-tetradecenal. The identification included the use of electroantennograms (EAG's) to monitor the isolation of the pheromone. This technique, based on the pioneering work of *D. Schneider* and his colleagues at Seewiesen, depends on the fact that electrical signals, generated by an isolated insect antenna as a result of receptor site activity, can be amplified and visualized by an oscilloscope or other suitable device. *Roelofs et al.* have used the EAG method to advantage in studying many lepidopterous attractants[136]. The pheromones of the tortricids *Paralobesia viteana*[156] and *Zeiraphera diniana*[157] have been characterized using the EAG technique in conjunction with classical structural analysis. *Birch* found the EAG approach unreliable for studying pheromones from male noctuid moths[158].

Roelofs et al.[159] characterized a female-derived sex attractant of the codling moth, *Laspeyresia* (=*Carpocapsa*) *pomonella*, as (*E*,*E*)-8,10-dodecadien-1-ol *(32)*. The identification was based primarily on EAG response and gas chromatographic comparison with certain standards. The synthetic compound is attractive to males both in the laboratory and in the field[159]. However, *McDonough et al.*[160] proposed structure *(33)*, (*Z*,*E*)-7-methyl-3-propyl-2,6-decadien-1-ol, for one of the attractants. They did not detect any (*E*,*E*)-8,10-dodecadien-1-ol *(32)* in the codling



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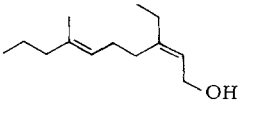


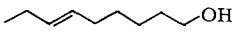
(33)

moths. The discrepancy between these results awaits resolution. *George* and *McDonough*[161] have reported that seven bioactive fractions, including *(33)*, can be obtained from female *L. pomonella*.

4.7. Diptera

There is evidence for pheromonal communication in numerous dipteran species, but only two pheromones have

been identified. *Carlson et al.*[162] characterized the sex attractant of the common housefly, *Musca domestica* (Muscidae), as (*Z*)-9-tricosene. Very recently, *Jacobson et al.*[163] identified two components of the male-derived sex pheromone of the Mediterranean fruit fly, *Ceratitis capitata* (Tephritidae), as (*E*)-6-nonen-1-ol *(34)* and methyl (*E*)-6-nonenoate *(35)*.



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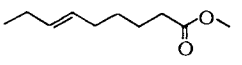

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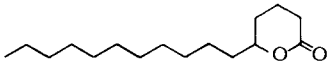
4.8. Hymenoptera

Although the order Hymenoptera is only about the third largest order of insects in terms of identified species, the volume of literature on pheromonal communication is larger than that of any other invertebrate group. Here pheromonal communication has attained its greatest development: for example, *Wilson* (see Ref. [42a], p. 218) states that most of the social organization of the fire ant *Solenopsis invicta* (= *Solenopsis saevissima richteri*, red form) may be mediated by as few as ten pheromones. Our discussion is limited to recent work on some hymenopteran pheromones of known chemical constitution (for detailed reviews see Refs. [42a, 59, 130, 164—171]).

Both isomers of citral have been identified[172] in the mandibular gland secretion of the bee *Hylaeus cressoni* (family Colletidae); dihydroambrettolide is responsible for the musk-like scent of the bees *Halictus albipes* and *H. calceatus* (family Halictidae)[173]. These compounds probably act as pheromones, but their precise functions are uncertain. The "queen substance" for the oriental hornet, *Vespa orientalis* (Vespidae) has been identified[174] as δ-hexadecalactone *(36)*. Some territorial marking pheromones of male bumblebees (*Bombus* species, family Bombidae) have been characterized as rather complex mixtures of terpenes, ethyl esters, acetates, and other compounds[175]. The main component of the marking scent of *B. terrestris* is 2,3-dihydrofarnesol ((*E*)-3,7,11-trimethyl-6,10-dodecadien-1-ol) *(37)*[176].



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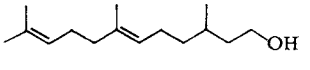


(37)

The queen substance for the honeybee, *Apis mellifera* (Apidae), (*E*)-9-oxo-2-decenoic acid, has recently been isolated from the three other species in this genus, *A. cerana*, *A. indica*, and *A. florea*[177], where it presumably serves the same functions as in *A. mellifera*. The sting pheromone, isopentyl acetate, is also shared by the four *Apis* species[178].

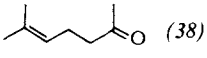
2-Heptanone, another bee alarm pheromone[179], occurs only in the mandibular glands of *A. mellifera*[178]. The Nassanoff gland, peculiar to the genus *Apis*, produces a secretion which contains several monoterpenoid compounds, the most attractive of which are reported to be the two isomers of citral[180]. Several functions for this secretion have been demonstrated (queen finding[181], marking of food sources[182]), but the full biological significance of the exudate probably remains to be established[167].

Nineteen analogs of (*E*)-9-oxo-2-decenoic acid have been evaluated as sex attractants for *A. mellifera*[183]. The specificity of the drone's receptor site is so extreme, that *any* modification of the molecule results in complete loss of activity. Similar experiments have been reported with analogs of the alarm pheromones, isopentyl acetate and 2-heptanone[184].

Citral has been identified[185] in the mandibular gland secretion of workers of the stingless bee *Trigona subterranea* (Apidae). Depending on concentration and context, the workers react in various ways when confronted with synthetic citral.

The literature on ant (Formicidae) pheromones is large and diverse. We shall concern ourselves here with only those pheromones whose structures have been elucidated in the past four to five years.

Pheromones have been implicated recently in the aggressive behavior of the Australian bull ant, *Myrmecia gulosa*, a member of the most primitive living subfamily of ants, Myrmeciinae[186]. *Cavill* and *Williams*[187] had identified several hydrocarbons in this species' Dufour's gland, but they do not appear to be involved in alarm or attack behavior[186].

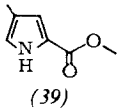


(38)

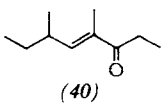
6-Methyl-5-hepten-2-one *(38)* has been known for some time to be an alarm pheromone for several Australian *Iridomyrmex* species (subfamily Dolichoderinae)[188]. It has recently been identified as an alarm pheromone component in an *Iridomyrmex* species from Florida, which raises some interesting chemotaxonomic questions since this group of ants has been identified with 2-heptanone[189].

The only identified pheromones in the subfamily Ponerinae are dimethyl sulfide and dimethyl trisulfide, identified in 1967[190] in the mandibular gland secretion of *Paltothyreus tarsatus*. These sulfides appear important in defense and in the communication of alarm.

Trail following is one of the most conspicuous activities of ants; in spite of much research, only one ant trail pheromone has been identified. The major component of the trail pheromone of the Texas leaf-cutting ant, *Atta texana* (Myrmicinae) was recently characterized as methyl 4-methylpyrrole-2-carboxylate *(39)*[191]. Several analogs of *(39)* have been synthesized and possess considerable trail pheromone activity[192]. In addition, the pyrrole may well be a component of the trail pheromone of other ants in this tribe (Attini)[193].



(39)



(40)

Many alarm pheromones are known from myrmicine ants. Among these are 3-octanone in the genera *Crematogaster*[194], *Myrmica*[195], *Acromyrmex*[196], and *Trachymyrmex*[196]; 6-methyl-3-octanone in *Crematogaster*[194d] and *Myrmica*[197]; (*E*)-2-hexenal in *Crematogaster*[194b]; and 4,6-dimethyl-4-octen-3-one *(40)* in *Manica*[198]. Sex pheromones have recently been demonstrated in some myrmicine ants[199].

Although formic acid has been known from ants for 300 years, only recently has it been shown to communicate alarm in the genera *Formica*[169] and *Camponotus*[200] (subfamily Formicinae).

The alarm pheromone of *Lasius spathepus* (Formicinae) has recently been characterized as *citronellal*[201]. This monoterpene aldehyde has also been detected in *L. flavus*[202], *L. carniolicus*[202], and *L. alienus*[203]. However, *n*-undecane appears to be the principal alarm pheromone for *L. alienus*[203]. Many other hydrocarbons and mono- and sesquiterpenes have also been reported in this genus[202–204]. The Dufour's gland secretion of *Anoplolepis custodiens* consists almost entirely of saturated and unsaturated normal hydrocarbons from C_{10} to C_{21}[205]; they do not, however, appear to be alarm pheromones. *Regnier* and *Wilson*[206] report that *n*-undecane serves as an alarm pheromone and as a spreading agent for formic acid in the formicine *Acanthomyops claviger*. The pheromones of the slave-making ants *Formica sanguinea*[207] and *Polyergus rufescens*[207b] have also been investigated. In these species, mixtures of simple aliphatic acetates serve as alarm pheromones. Finally, *Bergström* and *Löfqvist*[208] have identified 40 volatile compounds in the Dufour's gland secretion of *Camponotus ligniperda*. Included are *n*-alkanes, alkenes, alkadienes, alkanols, alkenols, several acetates, 2-pentadecanone, farnesene and farnesyl acetate. Formic acid and the *n*-alkanes from nonane to dodecane elicit alarm; *n*-tridecane, the most abundant component, elicits little if any alarm, but may function as a spreading agent.

5. The Future of Pheromones

Pheromones and attractants can be expected to play increasing roles in the integrated control of various insect pests. Although there have been some disappointing results, there have also been notable successes; further study of insect pheromones is surely justified from an economic and environmental standpoint. Nor should the continuing intellectual challenge be overlooked.

Chemically identified pheromones are known from only seven of the twenty-seven insect orders; but it would seem that intraspecific chemical communication may eventually be detected in every order. The study of insect pheromones will continue to occupy an exciting and relevant part of the chemical literature for many years to come.

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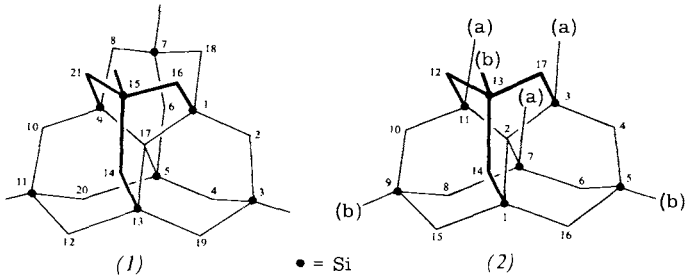
COMMUNICATIONS

Carbosilanes Having a New Silicon-Carbon Skeleton ("Silascaphanes"[**])

By *Gerhard Fritz, Gerwig Marquardt,* and *Heinz Scheer*[*]

Extensive separation of the pyrolysis products of tetramethylsilane (TMS)[1] (pyrolysis conditions: *ca.* 700 °C, gas phase) led to the discovery of a new type of carbosilane whose six-membered rings composed of alternating carbon and silicon atoms exist only in the boat form and which thus differ from the "carborundanes"[2] (sections of the ideal carborundum lattice as molecular skeleton with the SiC six-membered rings exclusively in the chair form).



(1) • = Si —• = Si–CH_3 *(2)*

We have isolated the compounds $Si_8C_{17}H_{36}$ *(1)* and $Si_7C_{16}H_{36}$ *(2)* as the first derivatives of this class.

The molecule of compound *(1)* has the symmetry of the space group $P\bar{4}3m\text{-}T_d^1$, possesses four threefold axes, and contains twelve six-membered rings made up of alternating Si and C atoms in the boat form (octasiladodecascaphane).

Compound *(1)* is obtained as white crystals of m. p. 265 °C. Precise determination of the relative molecular mass gave *m/e* 464.09613 (calc. for $Si_8C_{17}H_{36}^+$ 464.0971); the most intense peaks were for *m/e* 464 ($M=Si_8C_{17}H_{36}^+$) and 449 ($M-CH_3=Si_8C_{16}H_{33}^+$), as well as *m/2e* 217 ($[M-2CH_3]/2=Si_8C_{15}H_{30}^+/2$). The molecule contains four equivalent $SiCH_3$ groups and twelve equivalent Si_2CH_2 groups. Accordingly, the ^{1}H-NMR spectrum (solvent CCl_4) exhibits only two singlets at $\tau=9.91$ (Si—CH_3) and 10.24 (Si—CH_2—Si) in the intensity ratio 1:2. X-ray structure analysis[3] confirmed the structure of *(1)*.

Compound *(2)* contains one SiC unit less than the carbosilane *(1)* and thus lacks the possibility of optimum linkage to six-membered ring systems characteristic of the latter; *(2)* contains nine SiC six-membered rings in the boat form (heptasilanonascaphane). The molecule has one threefold axis.

Compound *(2)* is obtained as white crystals of m.p. 225–226 °C. Precise molecular mass determination: *m/e* 424.11999 (calc. for $Si_7C_{16}H_{36}^+$ 424.12018). ^{1}H-NMR (solvent CCl_4): two signals each in the $SiCH_3$ region ($\tau=9.80$ and 9.89) and in the Si_2CH_2 region ($\tau=10.20$ and 10.27). Mutual shielding leads to an upfield shift of the signal due to $SiCH_3$ groups (a) relative to $SiCH_3$ groups (b). Molecular models show that the three methylene groups of C atoms 14, 15, 16 and the six methylene groups of C atoms 4, 6, 8, 10, 12, 17 are mutually equivalent. Accordingly, the relative intensity ratio of the $SiCH_3$ proton signals amounts to 1:1 (9.0:8.7), and that of the Si_2CH_2 protons 1:2 (5.8:11.8).

The carbosilane *(2)* is an isomer of the carborundane *(3)*, which has already been obtained from the pyrolysis products of TMS[2], and of the compound *(4)* which we have now prepared for the first time.

The upper half of the molecule *(4)* has a Si-adamantane structure with SiC six-membered rings in the chair form while the lower half contains the three "side" SiC six-membered rings in the boat form. *(4)* thus represents a combination of the two structural types.

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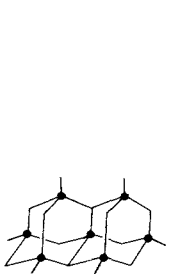
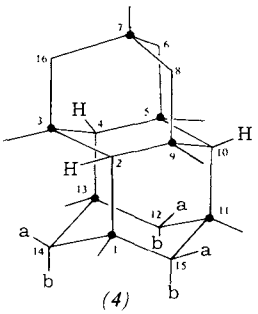
[**] Owing to the complexity of the IUPAC nomenclature we propose that such compounds with alternating fixed SiC six-membered rings in the boat form (Latin *scapha*) be known as "silascaphanes", *e.g.* 3,7,11,15-tetramethyl-1,3,5,7,9,11,13,15-octasiladodecascaphane, the numbering of the atoms agreeing with the official nomenclature.



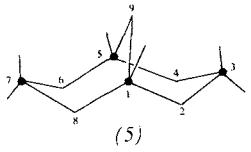
(3)



(4)

Compound *(4)* is obtained as white crystals of m. p. 240–242 °C. Precise mass determination for $M-CH_3$ ($M=Si_7C_{16}H_{36}^+$): *m/e* 409.09816 (calc. for $Si_7C_{15}H_{33}^+$ 409.0967). ^{1}H-NMR: three sharp signals in the $SiCH_3$ region ($\tau=9.71$, 9.74, and 9.77; in benzene). The protons of the CH_3 groups attached to Si atoms 1, 11, 13 are mutually equivalent and differ from those on Si atoms 3, 5, 9 which are also mutually equivalent. They all differ from the CH_3 group on Si atom 7 leading to a relative intensity ratio of 3:3:1. The signal of the Si_2CH_2 protons with C atoms 6, 8, 16 appears at $\tau=10.30$, and that of the Si_3CH protons on C atoms 2, 4, 10 at $\tau=10.84$ (both singlets); relative intensity ratio 2:1. The protons a and b on the C atoms 12, 14, 15 have different chemical environments so that an AM spectrum results ($\tau_A=10.55$, $\tau_M=9.87$; $J_{AM}=12.6$ Hz). The coupling is established by double resonance experiments. The 220-Hz spectrum clearly shows the AM pattern.

The simplest carbosilane having fixed SiC six-membered rings in the boat form is compound *(5)* (tetrasiladiscaphane which we have now also isolated from the pyrolysis products of TMS; SiCl-containing derivatives are known[4]. The compound has already been synthesized by another route[5].



(5)

The carborundanes predominate over the silascaphanes in the pyrolysis products of tetramethylsilane. On the basis of the C—C (1.54 Å) and Si—C (1.85 Å) distances in six-membered rings the boat form should be more stable for carbosilanes than for hydrocarbons.

Compounds *(1)* to *(5)* were isolated alongside other products by gas chromatography from the previously described[2] viscous pyrolysis products of $Si(CH_3)_4$ after preliminary work-up by column and gel chromatography.

Nomenclature[**]:

(1): 3,7,11,15-Tetramethyl-1,3,5,7,9,11,13,15-octasilaoctacyclo[7.7.1.1^{1,7}.1^{3,13}.1^{5,11}.1^{9,15}.0^{5,17}.0^{13,17}]heneicosane; *(2)*: 3,5,7,9,11,13-Hexamethyl-1,3,5,7,9,11,13-heptasilahexacyclo[7.5.1.1^{1,5}.1^{3,13}.0^{2,7}.0^{2,11}]heptadecane; *(4)*: 1,3,5,7,9,11,13-Heptamethyl-1,3,5,7,9,11,13-heptasilahexacyclo[9.3.1.1^{3,7}.0^{2,9}.0^{4,13}.0^{5,10}]hexadecane; *(5)*: 1,3,3,5,7,7-Hexamethyl-1,3,5,7-tetrasilabicyclo[3.3.1]nonane.

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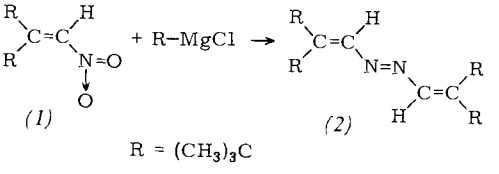
The First Divinylazo Compound and Its RadicalAnion[1]

By *Wilhelm Ahrens* and *Armin Berndt*[*]

Reaction of the nitroalkene *(1)*[2] with *tert*-butylmagnesium chloride afforded, in addition to several colorless products of undetermined constitution, orange crystals of a substance *(2)* which is very soluble in nonpolar solvents (light petroleum, benzene, CCl_4) but only sparingly soluble in polar solvents (acetonitrile, DMSO, ethanol). Mass spectroscopic elemental analysis revealed the composition $C_{20}H_{38}N_2$[3]. Since the NMR spectrum of *(2)* (in CCl_4, relative to TMS) only contains three singlets at $\delta=7.0$ (2H), 1.3 (18H), and 1.5 ppm (18H), two $C_{10}H_{19}N$ units must be linked together symmetrically. This observation and the similarity of the electronic excitation spectrum to that of azobenzene[4] indicate the constitution of a 3,8-di-*tert*-butyl-2,2,9,9-tetramethyl-5,6-diazadeca-3,5,7-triene (2,2′-di-*tert*-butyl-3,3,3′,3′-tetramethylazo-1-butene) for *(2)*. Compound *(2)* is the first divinylazo compound to be described. Unlike the thermolabile 1-phenylazo-1-alkenes[5], compound *(2)* can be sublimed at 180 °C under normal pressure without decomposition.



(1) + R–MgCl → *(2)*

R = $(CH_3)_3C$

The relatively low extinction coefficient of the n→π* excitation ($\varepsilon=232$ for $\lambda=440$ nm) and the high ε values of the π→π* excitation ($\varepsilon=18100$, 28400, and 28100 for $\lambda=337$, 322, and 313 nm respectively) suggest that the vinyl substituents on the azo group are *trans* configurated. *cis*-Configurated azoarenes[6] and alkylazoarenes[7] are characterized by relatively high ε values for the n→π* transition and relatively low ε values for the π→π* transition. The absence of any absorption at 230—240 nm apparent on comparison with the spectrum of azobenzene confirms the assignment of these bands to transitions of the phenyl groups[8].

In the Raman spectrum (in CCl_4) *(2)* gives a strong band at 1415 cm^{-1} and a broad band of medium intensity at 1567 cm^{-1} in the regions characteristic of N=N vibrations (1408—1447 and 1558—1579 cm^{-1})[9]. In acetonitrile *(2)* can be reduced electrolytically (tetra-*n*-propylammonium perchlorate as conducting salt) to the radical anion. Its ESR spectrum (Fig 1a) can be reconstructed with $a^N=5.1$ G (2N) and $a^H=2.0$ G (2H) (Fig. 1b). Under the same measuring conditions we found $a^N=5.0$ G (2N) (literature data: 4.84, 5.1, and 5.2 in various solvents[10])

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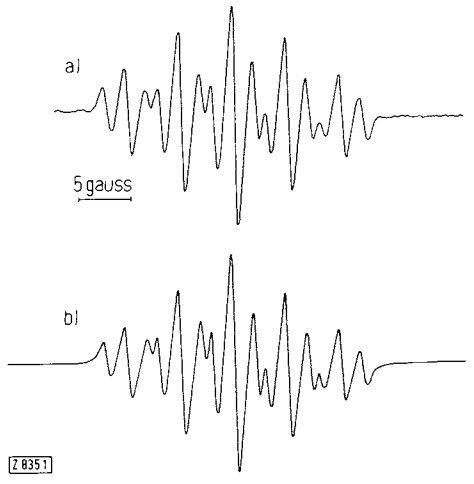

Fig. 1. a) ESR spectrum of the radical anion of *(2)* in acetonitrile at 25 °C; b) computer simulated spectrum with $a^N = 5.1$ G (2 N) and $a^H = 2.0$ G (2 H), line width 0.75 G.

for the radical anion of azobenzene. Assuming a direct proportionality between a^N and the spin density at the nitrogen ρ^N, which is justifiable in numerous cases, a proportionality constant Q^N of 16.5 G is obtained from $a^N = 8.25$ G for the radical anion of 2,2'-azoisobutane[11] and $\rho^N = 0.5$. Hence a value of $\rho^N = 0.31$ follows for the radical anion of *(2)*. The spin density at C_α is calculated as $|\rho_\alpha^C| = 0.085$ with the aid of the McConnell equation and the value of $Q_{C-H}^H = -23.7$ G generally valid for radical anions. The normalization condition $\sum_i \rho_i = 1$ thus yields a spin density of 0.28 at c_β, ρ_α^C being given a theoretically justified negative sign. HMO spin density calculations by the McLachlan method[12] with the parameters used for the azobenzene radical anion give $\rho^N = 0.30$, $\rho_\alpha^C = -0.10$, and $\rho_\beta^C = 0.30$ if the effect of the *tert*-butyl substituents is neglected.

In the mass spectrum of *(2)* which contains relatively few fragment ions the signal at $m/q = 153$ is particularly striking since it represents the base peak at electron impact above 20 eV and still has 80% of the intensity of the molecular ion at 16 eV whereas only the fragments M − 56 and M − 57 then have intensities above 5% (loss of *tert*-butyl radicals and of isobutylene respectively). The absence of a half integral signal at $m/q = 153.5$ proves that the peak at 153 (exact mass 153.1515) is not due to a doubly charged molecular ion but to an ion of composition $C_{10}H_{19}N^+$. In contrast to azobenzene, which preferentially fragments with cleavage of the C—N bond[13], *(2)* very readily cleaves at the N=N bond.

Attempts to convert nitroalkenes subject to less steric hindrance into the corresponding divinylazo compounds have so far been unsuccessful.

3,8-Di-tert-butyl-2,2,9,9-tetramethyl-5,6-diazadeca-3,5,7-triene (2):

A Grignard solution obtained from magnesium (1.46 g, 60 mmol) and *tert*-butyl chloride (5.56 g, 60 mmol) is slowly added dropwise to a solution of *(1)* (1.85 g, 10 mmol) in dry ether (4 ml) at −15 °C (ice/salt) under an inert gas. After 10 minutes' stirring of the cooled mixture it is hydrolyzed with aqueous ammonium chloride solution. The aqueous phase is extracted into ether; the combined ether extracts are twice washed neutral with water. After drying of the ethereal solution over magnesium sulfate and evaporation of the ether, part of the product *(2)* crystallizes. The filtrate is taken up in ethanol and a further crop of crystalline *(2)* is obtained in the cold. Recrystallizing twice from ethanol affords 56.1 mg (3.7%) of analytically pure *(2)* of m.p. 182—183 °C.

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[1] Reactions of Sterically Hindered Nitro Compounds, Part 3.—Part 2: *A. Berndt*, Tetrahedron Lett. *1970*, 173.—This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie, as well as by Chemische Werke Hüls and Deutsche Shell AG.

[2] *A. Berndt*, Tetrahedron *25*, 37 (1969).

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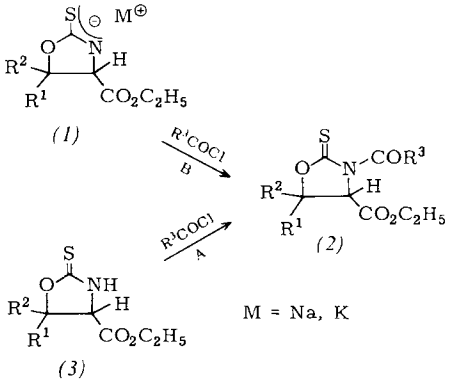
Ethyl 3-Acyl-2-thioxo-1,3-oxazolidine-4-carboxylates and Their Conversion into Ethyl α-(*N*-Acylamino)acrylates[**]

By *Dieter Hoppe*[*]

Ethyl 2-thioxo-1,3-oxazolidine-4-carboxylates *(3)* are formed in good yields by basic condensation of ethyl α-isothiocyanatoacetates with carbonyl compounds[1]. Their acylation with acyl halides in benzene/triethylamine at room temperature leads to ethyl 3-acyl-2-thioxo-1,3-oxazolidine-4-carboxylates *(2)*[2] (procedure A, see Table 1). The acyl compounds *(2)* are more conveniently obtained



directly from alkali metal salts *(1)* formed as primary products in the synthesis of *(3)*[1] by addition of acyl halides to the reaction mixture (procedure B).

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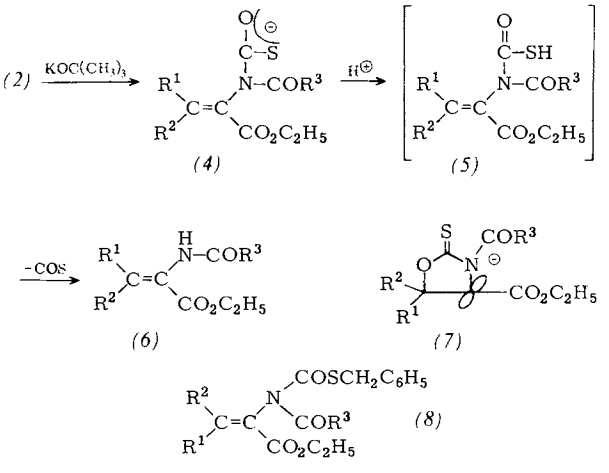
The structural assignment of *(2)* as *N*-acylation product follows from the IR spectrum: an intense absorption at 1770 cm^{-1} shows the compounds *(2a)*—*(2g)* to be urethanes; a C=N frequency at about 1600 cm^{-1} characteristic of the alternative oxazoline structure is not observed.

The acyl compounds *(2)* are converted into the ethyl α-(*N*-acylamino)acrylates *(6)* by treatment with potassium *tert*-butoxide (50% excess) in tetrahydrofuran at −60 °C and subsequent neutralization with glacial acetic acid (Table 1). *(6b)* and *(6f)* were obtained by heating *(2b)* and *(2f)* to 160—180 °C for 2 h with 5 mol-% of triethylammonium chloride.

All compounds *(6)* gave satisfactory CH analyses and were characterized by their IR and NMR spectra. Stereochemical assignments were based on the NMR spectra. Isomeric oxazolidinethiones *(2)* and aminoacrylates *(6)* can be separated by chromatography on silica gel with ether/light petroleum.

α-Acylaminoacrylic esters *(6)* are of significance for the preparation of unsubstituted[6] and β-functional α-amino-acids[7]; since not only R^1 and R^2 but also R^3 can be varied within wide limits, the amino protecting group can be adapted to subsequent synthetic steps from the very beginning of a reaction sequence.



The first detectable intermediate formed is *N*-acyl-*N*-vinylthiocarbamate *(4)* which is converted into the free thiocarbamic acid *(5)* on acidification and thence into the aminoacrylates *(6)* by loss of carbon oxide sulfide. *(4)* can be trapped, *e.g.* with benzyl bromide, as *N*-acyl-*N*-vinylthiourethane *(8)*.

Available evidence indicates a concerted ring cleavage[3]. Thus *trans-(2g)* gives exclusively *Z-(6g)*, while *cis-(2g)* affords predominantly *E-(6g)* (*E*/*Z* ≈ 3 : 1). A two-step process *via* the anion *(7)*—analogous to base-induced ring cleavage of oxazoline-[4] and 2-alkylthiooxazoline-4-carboxylic esters[5]—would give roughly equal product ratios starting from both isomers. Moreover, base-catalyzed H/D exchange could not be detected in oxazolidinethione. Isomerization of the thiocarbamic anion *E-(4g)*, as has been detected for *E-(4a)*, probably accounts for the incomplete stereospecificity of the reaction of *cis-(2g)*.

Diethyl 5,5-dimethyl-2-thioxo-1,3-oxazolidine-3,4-dicarboxylate (2b):

Route A: Ethyl chloroformate (2.17 g, 20 mmol) was added without cooling to a solution of ethyl 5,5-dimethyl-2-thioxo-oxazolidine-4-carboxylate[11] *(3b)* (4.06 g, 20 mmol) and triethylamine (2.15 g, 21 mmol) in benzene (50 ml) initially cooled to 0 °C. The mixture was then stirred for 30 min at room temperature and allowed to stand for 1 h at 0—5 °C before the triethylammonium chloride was filtered off and the solvent evaporated off in a water pump vacuum. The residue was recrystallized from tetrachloromethane and afforded 4.5 g of *(2b)*. IR (KBr): 1740, 1770 cm^{-1} (CO).—^{1}H-NMR ($CDCl_3$): τ = 5.35 (s, 4-H), 8.37 and 8.53 (both s, CH_3).

Ethyl cis- and trans-3-benzyloxycarbonyl-5-phenyl-2-thioxo-1,3-oxazolidine-4-carboxylate (2g):

Route B: A mixture of ethyl isothiocyanatoacetate (5.8 g, 40 mmol) and benzaldehyde (4.3 g) in tetrahydrofuran (10 ml) was added dropwise to a vigorously stirred solution of potassium *tert*-butoxide (4.5 g, 40 mmol) in dry tetrahydrofuran (50 ml) under nitrogen at −60 °C. Stirring was continued for 30 min at −60 °C and the mixture was then allowed to warm up to −20 °C whereupon benzyl chloroformate (6.9 g, 40 mmol) in a little tetrahydrofuran was run in. After 30 min the solvent was removed under water-pump vacuum in a rotary evaporator and the residue taken up in dichloromethane (100 ml) and ice-water (30 ml). Washing twice with water (2 × 30 ml), drying the solution over sodium sulfate, and evaporation of the solvent in a vacuum furnished 14.8 g of crude *(2g)* as a bright yellow

Table 1. Ethyl 3-acyl-2-thioxo-1,3-oxazolidinecarboxylates *(2)* and ethyl α-(*N*-acylamino)acrylates *(6)* synthesized.

				(2)			*(6)*	
	R^1	R^2	R^3	Yield [%]	M.p. [°C] (*cis/trans*)	Yield [%]	(*E*/*Z*)	M.p. [°C] (B.p. [°C/torr])
(a)	H	CH_3	$OCH_2C_6H_5$	45 [b, d]	(2.5:1)	85 [e]	1:4	*Z*: 71–72
(b)	CH_3	CH_3	OC_2H_5	84 [a, d]	86–87	71 [f, g]	—	(125/1.0)
(c)	CH_3	CH_3	$OCH_2C_6H_5$	66 [b, d]	103–104	80 [e]	—	37
(d)	H	$(CH_3)_2CH$	$OCH_2C_6H_5$	86 [b, c]	(1:1)	76 [e]	1:4	
(e)	CH_3	cyclo-C_3H_5	$OCH_2C_6H_5$	88 [b, e]	(1:1)	80 [e]	1:2	—
(f)	H	C_6H_5	OC_2H_5	98 [a, c]	(1:2.0)	60 [e, g]	1:4	*Z*: 107
(g)	H	C_6H_5	$OCH_2C_6H_5$	61 [b, d]	(1:2.5)	79 [e]	1:3.3	—
				39 [e]	(<5:100)	98 [c]	<5:100	*Z*: 58
				17 [e]	(100:<5)	98 [c]	3:1	—
(h)	C_6H_5	C_6H_5	C_6H_5	87 [a,d]	144–146	89 [d]	—	147

[a] Route A.
[b] Route B.
[c] Crude product.
[d] After purification by recrystallization.
[e] After chromatographic purification or separation of isomers.
[f] After purification by distillation.
[g] Prepared by thermolysis of *(2)*, see text.

oil. Crystallization with diethyl ether (100 ml) at 0 °C afforded 9.5 g of *(2g)* having m.p. 85—95 °C (*cis/trans* = 1 : 2.5), ^{1}H-NMR ($CDCl_3$): *cis-(2g)* $\tau = 4.12$ (d) and 4.84 (d) ($J = 9.5$ Hz, 5-H and 4-H), 6.44 and 9.32 ($AA'X_3$ part, OC_2H_5); *trans-(2g)* $\tau = 4.40$ (d) and 5.13 (d) ($J = 4.5$ Hz, 5-H and 4-H), 5.83 (q) and 8.83 (t) (OC_2H_5).

Ethyl E- and Z-α-(N-benzyloxycarbonylamino)cinnamate (6g):

(2g) (*cis/trans* = 1 : 2.5; 7.7 g, 20 mmol) in tetrahydrofuran (30 ml) was added dropwise to a vigorously stirred solution of potassium *tert*-butoxide (30 mmol) in dry tetrahydrofuran at −60 °C. After 30 min acetic anhydride was squirted into the mixture which was then permitted to warm to room temperature. The product was worked up as described for *(2g)* but with diethyl ether as solvent to give 6.5 g (100 %) of crude *(6g)* (*E/Z* = 1 : 3.3). Chromatography on an 80-fold amount (w/w) of silica gel (neutral) with light petroleum (40—60 °C)/ether (1 : 1) afforded 1.3 g (20 %) of *E-(6g)* ($R_f = 0.59$, TLC silica gel commercial films) as a colorless oil and 4.5 g (69 %) of *Z-(6g)* ($R_f = 0.44$) of m.p. 58 °C.—IR (film): 3300 (NH), 1680—1730 (C=O), 1640 (C=C), 1490 and 1520 cm^{-1} (amide II).—^{1}H-NMR ($CDCl_3$), *E-(6g)*: $\tau = 2.45$ (s, vinyl H), 2.90 (s, NH), 5.95 (q), and 9.05 (t) (OC_2H_5); *Z-(6g)*: $\tau = 2.55$ (s, vinyl H), 3.5 (s, NH), 5.80 (q), and 8.77 (t) (OC_2H_5).

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[1] *D. Hoppe*, Angew. Chem. *84*, 956 (1972); Angew. Chem. internat. Edit. *11*, 933 (1972).

[2] If attack at the nitrogen is sterically hindered, as *e.g.* in the case of ethyl *cis*-4-methyl-5-phenyl-2-thioxo-1,3-oxazolidine-4-carboxylate [$R^1 = C_6H_5$, $R^2 = H$, CH_3 in place of H in *(3)*] then *S*-alkylation is observed under the experimental conditions given. Above 100 °C 2-acylthio-1,3-oxazoline isomerizes to the *N*-acyl compound *(2)*.

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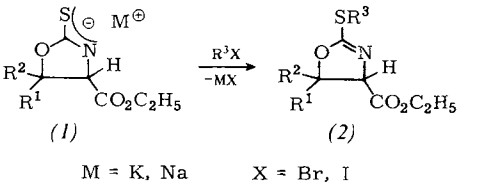
[7] For the synthesis of cysteine derivatives see: *U. Schöllkopf* and *D. Hoppe*, Angew. Chem. *82*, 253 (1970); Angew. Chem. internat. Edit. *9*, 236 (1970).

2-Alkylthio-2-oxazoline-4-carboxylic Esters and Their Conversion into α-(*N*-Alkylthiocarbonylamino)acrylic Esters[**]

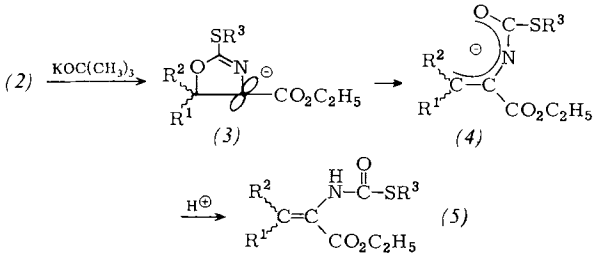
By *Dieter Hoppe*[*]

Whereas acylation of ethyl 2-thioxo-1,3-oxazolidine-4-carboxylates[1] or their ambidentate anions *(1)* leads to 3-acyl-1,3-oxazolidine-2-thiones[2], alkyl halides attack the sulfur atom to yield ethyl 2-alkylthio-2-oxazoline-4-carboxylates *(2)*.

The oxazolines *(2)* are obtained without intermediate isolation when ethyl isothiocyanatoacetate and carbonyl compounds are treated with potassium *tert*-butoxide or sodium hydride in tetrahydrofuran[1] and the resulting salts *(1)* are allowed to react with alkyl halides. The oxazoline structure follows from the strong IR band at 1600 cm^{-1} (C=N).



The 2-alkylthiooxazolines *(2)* are anionized α to the carbonyl group by strong bases such as potassium *tert*-butoxide in tetrahydrofuran at −60 °C. The anions *(3)* undergo ring cleavage[3] yielding the *S*-alkyl-*N*-vinylthiourethane anion *(4)*. After acidification with acetic anhydride the ethyl α-(*N*-alkylthiocarbonylamino)acrylates *(5)* can be isolated by chromatography or crystallization (Table 1).



Diastereomeric oxazolines [$R^1 \neq R^2$ in *(2)*] yield *E/Z* mixtures of aminoacrylates *(5)* that are readily separated by chromatography on silica gel with ether/light petroleum. Expectedly, ring cleavage is not stereospecific: thus *trans-(2e)* gives the acrylic ester *(5e)* in an *E/Z* ratio of 1 : 3.3. Compounds *(5)* are of potential interest as reactants for amino acid synthesis, particularly since the alkylthio group can be removed selectively[4].

The aminoacrylic esters gave satisfactory CH analyses. They were characterized by their NMR and IR spectra [3300 (NH), 1710—1720 (CO_2R), 1640 and 1500 (NCOSR) and 1600—1650 cm^{-1} (C=C)].

Ethyl 2-benzylthio-5,5-dimethyl-2-oxazoline-4-carboxylates (2b):

A mixture of ethyl isothiocyanatoacetate (5.8 g, 40 mmol) and acetone (2.4 g, 40 mmol) in tetrahydrofuran (20 ml)[1] was added dropwise over 30 min to a stirred suspension of finely divided sodium hydride (0.98 g, 40 mmol) in anhydrous tetrahydrofuran at 20—30 °C under nitrogen. Stirring was continued at this temperature until evolution of hydrogen had ceased (1 h), the mixture cooled to −20 °C, and after removal of the cooling bath benzyl bromide was added (6.8 g, 40 mmol). After 30 minutes' stirring at room temperature the solvent was evaporated off in a water pump vacuum and the residue taken up in chloroform (100 ml) and ice-water (30 ml). Washing was repeated twice with water (2 × 30 ml), the chloroform solution dried over sodium sulfate and concentrated in a rotary evaporator. Distillation afforded 9.0 g of *(2b)*.—IR (film): 1735 (C=O), 1590 cm^{-1} (C=N).—^{1}H-NMR (CCl_4): $\tau = 5.82$ (s, 4-H), 8.54 (s), and 8.74 (s) (gem. CH_3).

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[**] This work was supported by the Deutsche Forschungsgemeinschaft.

Table 1. Ethyl 2-alkylthio-2-oxazoline-4-carboxylates *(2)* and ethyl α-(*N*-alkylthiocarbonylamino)acrylates *(5)* synthesized.

					(2)		*(5)*	
	R^1	R^2	R^3	X	Yield [%]	B.p. [°C/torr] (*cis/trans*)	Yield [%]	M.p. [°C] (*E/Z*)
(a)	CH_3	CH_3	CH_3	I	65 [a, c]	83–86/0.5	47 [d]	77–77.5
(b)	CH_3	CH_3	$CH_2C_6H_5$	Br	77 [b, c]	130–135/0.05	80 [d]	91.0–91.5
(c)		$-(CH_2)_4-$	$CH_2CH{=}CH_2$	Br	71 [a, c]	120–125/0.1	47 [d]	61
(d)		$-(CH_2)_5-$	$CH_2C_6H_5$	Br	78 [a, e]	—	70 [e]	76.5–77.0
(e)	H	C_6H_5	CH_3	I	98 [a, f]	(1:2.3)	82 [d]	(1:3.0)
	H	C_6H_5	CH_3	I	56 [e]	(<5:100)	98 [f]	(1:3.3)

[a] With potassium *tert*-butoxide.
[b] With sodium hydride.
[c] After purification by distillation.
[d] After purification by recrystallization.
[e] After purification by chromatography.
[f] Crude product.

Ethyl α-(N-benzylthiocarbonylamino)-β,β-dimethylacrylate (5b):

(2b) (5.8 g, 20 mmol) was added dropwise to potassium *tert*-butoxide (3.4 g, 30 mmol) in anhydrous tetrahydrofuran (30 ml) under nitrogen with stirring at −60 °C. After 30 min acetic anhydride was squirted in and the cooling bath removed. The product was worked up as for *(2b)* but with diethyl ether (100 ml) as solvent to give 5.4 g (93%) of crude *(5b)* (white needles). Recrystallization from light petroleum (40—60 °C)/ether (2:1) furnished 4.6 g (80%) of *(5b)*.—IR (KBr): 3230 (NH), 1720 and 1630 (C=O), 1500 (amide II), and 1640 cm^{-1} (C=C).—^{1}H-NMR ($CDCl_3$): τ = 3.2 (s, NH), 7.85 and 8.15 (both s, CH_3).

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[1] *D. Hoppe*, Angew. Chem. *84*, 956 (1972); Angew. Chem. internat. Edit. *11*, 933 (1972).

[2] *D. Hoppe*, Angew. Chem. *85*, 659 (1973); Angew. Chem. internat. Edit. *12*, 656 (1973).

[3] To be regarded as electrocyclic ring cleavage of a "cyclopentenyl anion" to give a "pentadienyl anion"; see *U. Schöllkopf, F. Gerhart, R. Schröder*, and *D. Hoppe*, Liebigs Ann. Chem. *766*, 116 (1972).

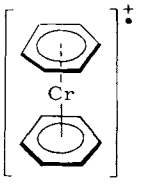
[4] For a review see *E. Schröder* and *K. Lübke*: The Peptides. Academic Press, New York 1965, Vol. 1, p. 41.

ESCA Investigations of Bis(arene)chromium Complexes

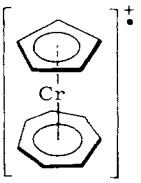
By *Herbert Binder* and *Ch. Elschenbroich*[*]

He(I) photoelectron spectra have been reported for symmetrical and unsymmetrical bis(arene)chromium complexes[1], but there have been no previous measurements of the corresponding X-ray photoelectron (ESCA) spectra[2] which could provide valuable information about the intramolecular charge distribution. We now report ESCA investigations [measurements were performed on an A.E.I. ES-100 photoelectron spectrometer, Al-K$\alpha_{1,2}$ radiation (1486.6 eV)] for the π-complexes *(1)*—*(5)*.

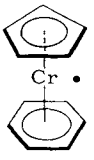
Chemical shifts δE_B can be determined from the measured electron-binding energies E_B and from the former it is possible in principle to describe the electronic environments of atoms in the molecules. We were especially interested in the charge distribution between the central metal and aromatic ligands as a function of ring size. The complexes *(1)*—*(5)*, however, yield only one, unstructured line (line width 1.7 eV) for the C1s level. Clearly the π-bonded ligands C_nH_n ($n = 5$, 6, or 7) differ in δE_B by an amount less than 0.5 eV, from which the limit for the difference in charges on the ligands C_5H_5 and C_7H_7 can be estimated: since a whole positive charge localized on a C atom leads to a shift δE_B of *ca.* 5 eV for the C1s level[4], complete charge separation $(C_5H_5)^{\delta-}Cr(C_7H_7)^{\delta+}$ ($\delta = 1$) would, it is to be expected, lead to a difference of about 1.7 eV between the C1s binding energies for the ligands cyclopentadienyl (δE_B(C1s) = −5/5 = −1.0 eV) and cycloheptatrienyl (δE_B = +5/7 = +0.7 eV). The fact that for *(5)* these C1s binding energies differ by <0.5 eV indicates that $\delta < 1/3$. Thus the charge distribution between the ligands in unsymmetrical sandwich complexes of chromium is largely equalized, which accords with the low dipole moment of 0.8 D[5] and with ^{1}H-NMR results[6].



(1a), counter ion $[B(C_6H_5)_4]^-$
(1b), counter ion $[PF_6]^-$



(2a), counter ion $[B(C_6H_5)_4]^-$
(2b), counter ion $[PF_6]^-$



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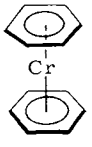

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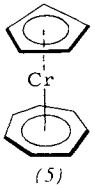

(5)

Table 1 contains the E_B values for the Cr2p$_{1,2}$,Cr2p$_{3,2}$ (spin orbit doublet) and for the Cr3p and Cr3s levels as well as the line widths for Cr2p$_{3/2}$ and the observed Cr3s multiplet splittings[7,8]. Since the C1s binding energies for the complexes *(1)*—*(5)* are equal within experimental error, the total charges on the complexes show the Cr binding energies to be divisible into two groups *(1)*—*(2)* and *(3)*—*(5)*. This confirms previous ESR findings[9] according to which one electron is removed from an MO

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with predominant Cr3d character in the transition $(arene)_2Cr^0 \rightarrow [(arene)_2Cr^I]^+$

Table 1. Electron binding energies E_B [a] for the complexes *(1)*—*(5)*.

	Line width					
	$Cr2p_{1/2}$ [eV]	$Cr2p_{3/2}$ [eV]	$Cr2p_{3/2}$ [eV]	Cr3s [eV]	$\Delta E_{Cr3s/Cr3d}$ [eV]	Cr3p [eV]
(1a)	586.7	577.7	2.5	79.0		46.6
				76.8	2.2	
(1b) [b]						
(2b)	586.2	577.1	1.7	79.5		46.5
					2.3	
				77.2		
(2a)	586.8	577.3				
(3)	585.5	576.3	1.8	76.9	1	45.4
(4)	584.8	575.7	1.7	76.7	—	45.4
(5)	585.3	576.0	1.5	77.1	—	45.7
Cr metal	—	—	—	—	—	44.8 [10]

[a] Referred to $E_B(C1s) = 286.6$ eV [3].
[b] Decomposition during measurement (binding energies and multiplet splitting identical with those for CrF_3 [8]).

If the Cr binding energies shown in Table 1 are compared with the corresponding value for Cr metal (reduced)[10] and with the results of *Carlson et al.*[8] for a series of Cr compounds, it is evident that the Cr atom carries a partial positive charge in the π-complexes *(1)*—*(5)*. Thus the central atom is the positive end of the bonding dipole metal-aromatic ligand also in the neutral complexes *(3)*—*(5)*. The acceptor character ($Cr3d \rightarrow C_nH_n$, π*) of the ligands is greater than their donor character (Cr3d, $4s \leftarrow C_nH_n$, π). The same result is derived from recent semiempirical[11] and *ab-initio*[12] MO calculations. For the two isoelectronic complexes *(4)* and *(5)* the larger E_B(Cr) value of *(5)* indicates more pronounced π*-acceptor properties for the unsymmetrical ligand combination π-C_5H_5|π-C_7H_7 than for the symmetrical combination π-C_6H_6|π-C_6H_6.

It can further be recognized from the Cr binding energies ($2p_{1/2}$, $2p_{3/2}$, 3s, 3p) that *(3)* belongs unambiguously to the group of Cr^0 complexes in respect to the intramolecular charge distribution although it can be formally described as a $Cr^I(d^5)$ complex.

Removing a 3s electron from a paramagnetic molecule leads to conditions of various spin multiplicities which differ in energy (multiplet splitting) according to the different values of the exchange integral.

Table 2. Comparison of ESR and ESCA data for the complexes *(1)*—*(3)*.

	(2)	*(1)*	*(3)*
$a(^{53}Cr)$ [G]	19.0	18.1	14.7
ΔE(Cr3s-3d) [eV]	2.3	2.2	<1
$E_B(Cr2p_{1/2})$[eV]	586.8	586.7	585.5

In Table 2 the ESR hyperfine coupling constants[13] $a(^{53}Cr)$ and the binding energies $E_B(Cr2p_{1/2})$ are compared with the ESCA multiplet splittings ΔE(Cr3s-3d). Both the ESR coupling constants and the ESCA multiplet splittings decrease with decreasing charge on the central atom, which corresponds to increasing delocalization of the unpaired $Cr3d_{z^2}$ electron. A correlation of this type between ΔE(Cr3s-3d) and $a(^{53}Cr)$ appears reasonable, if one considers that the isotropic hyperfine interaction of the unpaired electrons of *(1)*—*(3)* (which have predominant $Cr3d_{z^2}$ character[9]) depends on the size of the exchange integral between $3d_{z^2}$ and 3s, since the spin density of a d orbital can be transferred to the Cr nuclear position only by polarization of the inner s shells.

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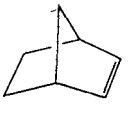
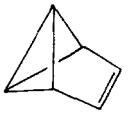
Cycloadditions of Benzvalene

By *Manfred Christl*[*]

Olefins having a strained double bond display a pronounced reactivity in numerous cycloadditions. The Diels-Alder additions[1,2] and 1,3-dipolar cycloadditions[3] of norbornene *(1)* may be cited as examples. Steric conditions similar to those in *(1)* prevail in benzvalene[4], presumably with even greater strain. *(2)* should therefore exhibit comparable dipolarophilic and dienophilic activity. The question then arises: How does the bicyclobutane system behave?



(1)



(2)

Dissolution of the stable 2,4,6-trimethylbenzonitrile oxide[5] in an ethereal solution of *(2)* afforded 98% of colorless *(3a)*, m.p. 101—103 °C[6], after 15 h at room temperature. Structural information was provided by the ^{1}H-NMR spectrum (Table 1) in which the absorptions of the mesityl group are accompanied by the characteristic signals of the protons in positions 1 and 6 of the 2-isoxazoline system[7] and a four-proton multiplet. The absence of signals due to olefinic protons suggests that the bicyclobutane system remains intact.

Reaction of benzonitrile oxide with *(2)* by the *in-situ* method[8] gave 88% of *(3b)* (m.p. 106—108 °C; NMR, see Table 1).

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Table 1. NMR signals of compounds *(3a)*, *(3b)*, *(4)*, *(5)*, *(6)*, *(8)*, and *(9)*: δ values [ppm], TMS internal standard, coupling constants in Hz.

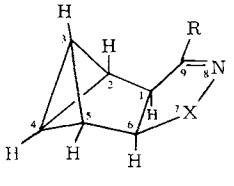
Cpd solvent	1-H	6-H	$J_{1,6}$	2-H	5-H	$J_{2,5}$	3-H	4-H	$J_{3,4}$	Other protons
(3a) CCl_4	3.64 br.d	4.94 br.d	8.5	2.0 to 2.6 m						mesityl: 6.78 (2H) br. s; 2.27 ($3CH_3$) s
(3b) CCl_4	3.79 br.d	4.98 br.d	7.9	2.48 br.s			2.05 and 2.20 br. AB-system		≈9	C_6H_5: 7.1—7.9 m
(4) [a] $CDCl_3$	3.89 m	4.56 m	9.2	2.58 and 2.74 m		4.75	1.93 and 2.19 m		9.1	$2C_6H_5$: 6.6—8.0 m
(5) [b] $CDCl_3$	4.13 m	5.00 m	9.1	2.67 and 2.80 m		4.75	1.95 and 2.13 m		8.9	C_6H_5: 6.8—7.4 m
(6) CCl_4	[c]	5.00 m		[c]			[c]			9-H_2: 3.5—4.3 m
(8) $CDCl_3$	3.14 br.s			2.85 m			2.03 and 2.47 AB-system		9.5	$2OCH_3$: 4.05 s
(9) [d] C_6C_6	1.86 m			2.02 m			2.52 m	2.27 m	8.0	

[a] $J_{2,3} \approx J_{2,4} \approx J_{3,5} \approx J_{4,5} \approx 1.8$ Hz. All other coupling constants are < 1.5 Hz.
[b] $J_{2,3} \approx J_{2,4} \approx J_{3,5} \approx J_{4,5} \approx 1.9$ Hz.
[c] 1-H to 5-H give rise to a multiplet between 1.5 and 2.3 (4H) and a multiplet at 2.66 (1H).
[d] $J_{2,3} = J_{3,5} = 1.05$ Hz; $J_{2,4} = J_{4,5} = 2.4$ Hz.

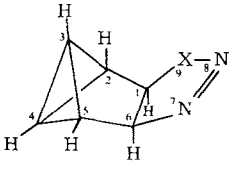
Diphenylnitrilimine[9] reacted with *(2)* to give a quantitative crude yield of the yellowish product *(4)*, m.p. 171—173 °C. In the NMR spectrum (Table 1) the signals of 1-H and 6-H appear in a region typical of 2-pyrazoline protons[7]. The coupling constants of the protons on the bicyclobutane skeleton are in good qualitative agreement with those of bicyclobutane itself[10]. Phenyl azide and *(2)* afforded a good yield of the colorless triazoline *(5)* (m.p. 116 °C, NMR, see Table 1).

Diazomethane and *(2)* gave 32% of the colorless liquid 1-pyrazoline *(6)* [b.p. 55—60 °C (bath)/0.1 torr; UV(cyclohexane): $\lambda_{max} = 330$ nm ($\varepsilon = 280$); NMR, see Table 1].

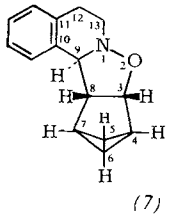
Reaction of 3,4-dihydroisoquinoline *N*-oxide and *(2)* furnished a crude yield of 95% of *(7)* [m.p. 143—145 °C (dec.). NMR ($CDCl_3$): δ = 7.15—7.60 (m, 4 aromatic H), 5.05 (br. d, 3-H); $J_{3,8} = 7.6$ Hz; 4.35 (br. d, 9-H), $J_{8,9} = 6.3$ Hz; 2.75—3.60 (m, 5H), 2.00—2.75 (m, 4H)].



(3a), X = O, R = Mesityl
(3b), X = O, R = C_6H_5
(4), X = N-C_6H_5, R = C_6H_5



(5), X = N-C_6H_5
(6), X = CH_2



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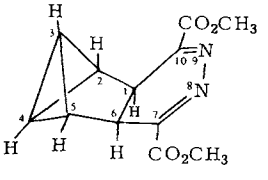
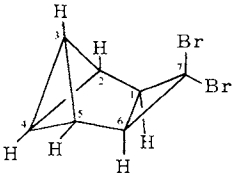


(8)

The reaction of 3,6-bis(methoxycarbonyl)tetrazine with *(2)* was accompanied by vigorous evolution of nitrogen and gave 65% of the orange compound *(8)*, m.p. 104—108 °C. The NMR spectrum (see Table 1) indicates the predicted c_s symmetry.



(9)

Dibromocarbene[11] added to *(2)* to give a 19% yield of the liquid quadricyclic compound *(9)*, b.p. 55—60 °C (bath)/0.1 torr. The c_s symmetry can be deduced from the NMR spectrum (see Table 1). The assignment is based on a 0.4 Hz long-range coupling of 4-H with 1-H and 6-H (M mechanism[12]) which is not found for 3-H owing to the less favorable steric arrangement of the bonds.

The simplicity of the above reactions opens up a route to a wide range of quadricyclic compounds. The highly strained bicyclobutane system should confer interesting properties upon them. This aspect is currently under study.

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CIDNP Evidence for Divergent Behavior of Singlet and Triplet Radical Pair Encounters in the Photo-Claisen Rearrangement

By *Waldemar Adam, Hanns Fischer, Hans-Jürgen Hansen, Heinz Heimgartner, Hans Schmid*, and *Hans-Rudolf Waespe*[*]

The detection of *meta* product[1] besides the usual *ortho* and *para* products[2] in the photo-Claisen rearrangement offers a unique opportunity to explore the possibility of divergent behavior of triplet *versus* singlet radical pair combinations as a result of the phases of the spin density distributions[3] of the radical pairs involved. Consequently, at least in principle the necessity of an escape reaction in the radical pair theory of Chemically Induced Dynamic Nuclear Polarization (CIDNP)[4] could be obviated.

In this communication we demonstrate that the photo-Claisen rearrangement of *p*-cresyl β-methallyl ether *(1)*, analogous to the related photo-Fries process[5], indeed involves radical pair intermediates and suggest that our findings of triplet encounters affording *meta* and singlet encounters affording *ortho* and *para* coupling products reflect divergent singlet-triplet radical pair behavior.

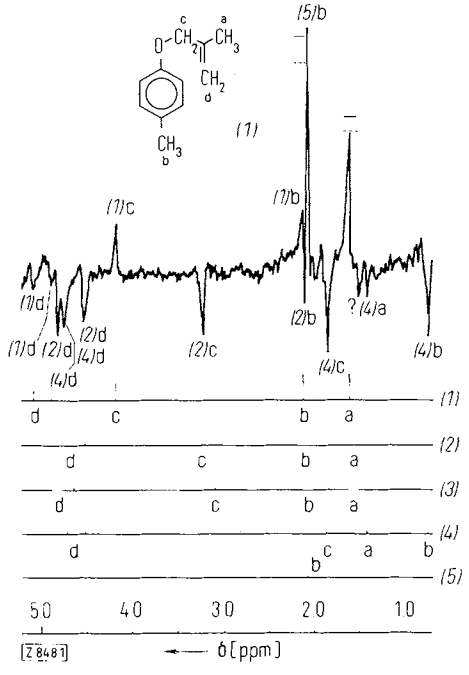

Fig. 1. CIDNP effects in the photo-Claisen rearrangement of *p*-cresyl β-methallyl ether *(1)* in benzene. Horizontal bars above the polarized spectrum of *(1)* indicate intensity of resonances before (——) and after (– – –) irradiation. Vertical lines below polarized spectrum indicate the position of the resonances of the authentic products *(1)*—*(5)* (TMS standard). *(1)* d, *(2)* c, *etc.* denote H^d of *(1)*, H^c of *(2)*, *etc.*

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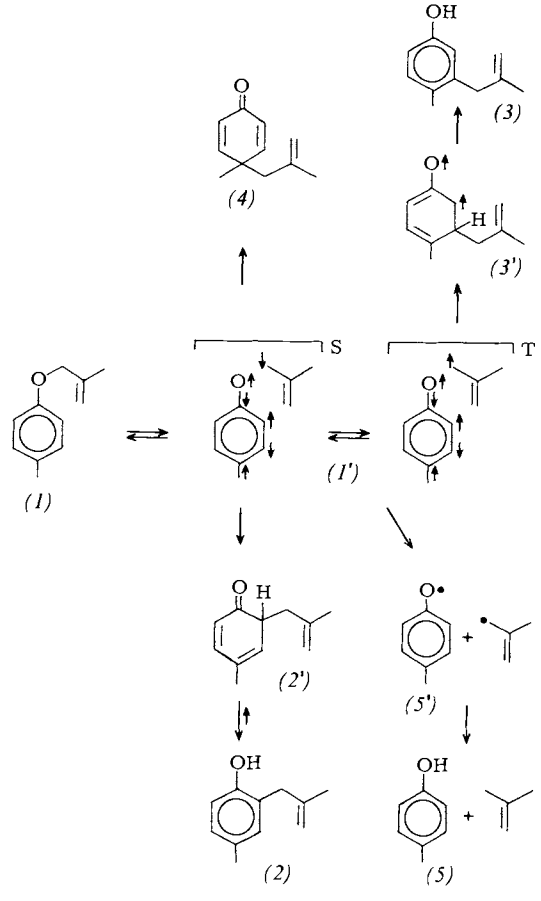
When a solution of *p*-cresyl β-methallyl ether *(1)* in benzene was irradiated in a quartz tube directly in the Varian HA-100 D NMR spectrometer with an unfiltered 1000 W mercury arc, the polarized spectrum in Figure 1 was observed. In terms of stick diagrams the resonances for each of the authentic photo-products are specified in δ(ppm) relative to TMS for the reformed ether *(1)*, the *ortho*, *meta*, and *para* products *(2)*, *(3)*, and *(4)*, respectively, and the cleavage phenol *(5)*. Control experiments revealed that irradiation of each of the authentic photoproducts *(2)* through *(5)* in C_6H_6 did not lead to the CIDNP effects displayed in Figure 1, demonstrating that the photo-Claisen rearrangement, analogous to the related photo-Fries process[5], proceeds *via* a radical pair mechanism (Scheme 1).



Scheme 1. Radical cage mechanism for the polarized products of the photo-Claisen rearrangement of *p*-cresyl β-methallyl ether *(1)*.

In view of the limitations of benzene for the detection of the *meta* product *(3)* due to severe overlapping of resonances, we examined the photolysis of *(1)* in a variety of polar and nonpolar solvents. The CIDNP results in these solvents paralleled those in benzene, but those in methanol and methyl formate were particularly informative since the resonances of the *p*-methyl protons (H^b, see Fig. 1) were now sufficiently resolved to observe the polarization of all products. The CIDNP effects in methanol (spectrum A) and methyl formate (spectrum C) are exhibited in Figure 2. Again the stick diagrams below each spectrum show the chemical shifts relative to TMS of the respective authentic products. Surprising is the fact that the polarization

of the *p*-methyl protons (H^b) of the *meta* product *(3)* is in the opposite sense of that for the *p*-methyl protons of the *ortho* and *para* products *(2)* and *(4)* respectively (see spectra A and C in Fig. 2).

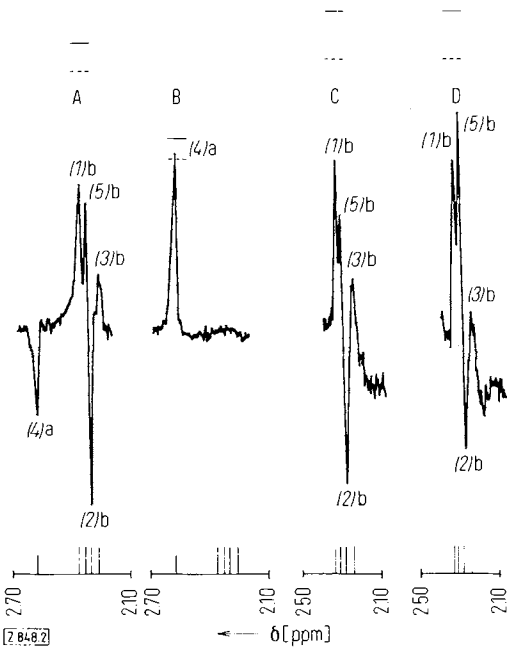


Fig. 2. CIDNP effects in the photo-Claisen rearrangement of *p*-cresyl β-methallyl ether *(1)* in methanol (spectrum A), of 4-(β-methallyl)-4-methyl-2,5-cyclohexadienone *(4)* in methanol (spectrum B), of *(1)* in methyl formate without (spectrum C) and with tri-*n*-butyltin hydride (spectrum D). The horizontal and vertical lines have the same meaning as in Fig. 1.

To exclude the possibility that the polarization of the *meta* product *(3)* arises from secondary reactions of the photo-labile *para* product *(4)*, we performed a control experiment by irradiating a 0.10 M methanolic solution of authentic cyclohexadienone *(4)* under the conditions of the photolysis of the Claisen ether *(1)* in methanol. Although *(4)* was considerably more rapidly photo-consumed than *(1)*, under comparable conditions of *ca.* 10% conversion no polarized products *(1)* to *(5)* could be detected in the photolysis of *(4)* by NMR monitoring of the methyl protons of the *para* product *(4)* and the *p*-methyl protons (H^b) of *(1)*, as shown in spectrum B of Figure 2. Finally, to eliminate the possibility that the *meta* product *(3)* is formed *via* free radicals, we irradiated a 0.025 M solution of *(1)* in methyl formate in the presence of 0.05 mol/l of tri-*n*-butyltin hydride (TBTH) radical scavenger[6] under identical conditions as for the first experiment. As spectrum D in Figure 2 demonstrates, the polarization of the *p*-methyl protons (H^b) of the *meta* product *(3)* could not be scavenged (even up to 0.10 mol/l TBTH) although the same degree of polarization for the *p*-methyl protons of *(1)* and *(2)* was achieved. It has been established that allyl radicals can be scavenged by TBTH[7]. Yet the *p*-methyl protons (H^b) of the *p*-cresol *(5)* exhibited a substantially larger polarization in the presence of TBTH. Thus, the TBTH scavenging experiment signifies that the *meta* product *(3)* must be principally formed from the primary pair like the Claisen ether *(1)* and the *ortho* and *para* products *(2)* and *(4)*, respectively; but the *p*-cresol *(5)* must be predominantly a radical scavenged product.

With the help of *Kaptein*'s formula for net polarization[8] and the ESR parameters for the related phenoxyl and allyl radicals[9], we find perfect agreement between experiment and theory if we assume that $\mu<0$ (singlet radical pair), $\varepsilon>0$ (pair products) for the Claisen ether *(1)*, *ortho* and *para* products *(2)* and *(4)*, respectively, and $\varepsilon<0$ (escape product) for *p*-cresol *(5)*, as in the case of the photo-Fries rearrangement[5]. However, the polarization of the *meta* product *(3)*, which does not arise *via* secondary processes of the *para* product *(4)* and cannot be scavenged by TBTH, must also be that of a primary pair process, though it is opposite (A) to the normal E polarization of the other pair products *(1)*, *(2)*, and *(4)*.

To account for this novel result, we combine the explanation for the divergent behavior of singlet and triplet states of β,γ-unsaturated ketones[3] with the current radical pair theory of CIDNP[4], and suggest the mechanism shown in Scheme 1. Phenoxyl-allyl radical pairs *(1')* are formed from the excited singlet state of *(1)*. Nuclear spin dependent interactions and *g*-factor differences cause the singlet *(1'S)* and triplet *(1'T)* character of the pairs to become nuclear spin and time dependent. From the spin distributions in the phenoxyl and allyl radicals[9] (Scheme 1) it is evident that radical pairs which are in state *(1'S)* at the instant of reencounter are likely to give the pair products *(1)*, *(4)*, and *(2)*, the latter *via* its tautomer *(2')* in a time interval short enough to preserve its nuclear polarization. Yet, radical pairs which are in state *(1'T)* during the reencounter cannot give products *(1)*, *(2)*, and *(4)* directly in view of unfavorable spin pairing but have the opportunity to combine at the *meta* position forming the triplet diradical *(3')* or to separate and eventually give escape products *(5)*. The triplet diradical *(3')* rearranges to the *meta* product *(3)* under spin inversion on a time scale preserving its nuclear polarization as in the *(2')*→*(2)* conversion.

It should be stressed that our mechanism (Scheme 1), suggested here to account for the opposite polarizations of *(1)*, *(2)*, and *(4) versus (3)* and *(5)* in terms of the divergent singlet-triplet radical pair coupling, permits the observation of CIDNP effects in systems *without escape reactions*[4]. Of course, our CIDNP results do not rule out minor concurrent paths leading to non-polarized products.

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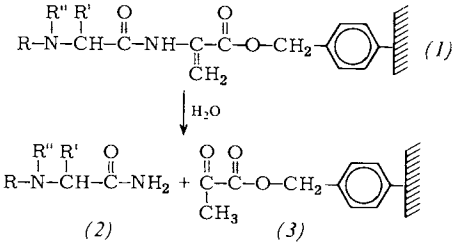
Solid Phase Synthesis of Peptides with Carboxyl-Terminal Amides—Thyrotropin-Releasing Factor (TRF)[**]

By *Erhard Gross*, *Kosaku Noda*, and *Bruce Nisula*[*]

Dedicated to Professor Theodor Wieland on the occasion of his 60th birthday

The α,β-unsaturated amino acid dehydroalanine[1] $H_2C{=}CNHR{-}COOH$, R = acyl or aminoacyl, may be employed in various ways in the solid phase synthesis of peptides[4]. It may, for instance, act as vehicle for the attachment of peptides to insoluble supports [see *(1)*] and/or donate its nitrogen to amide groups [see *(2)*][5]. The latter occurs under acidic conditions in the presence of equimolar ratios of water and may be invoked once the desired number of amino acid residues has been added to the growing peptide chain.



(1)

(2) *(3)*

(1a), R = Boc; R′ = R″ = H
(1b), R = Boc-leucylalanyl, R′ = R″ = H
(1c), R = Boc; R′—R″ = —CH_2—CH_2—CH_2—
(1d), R = Boc-pyroglutamylhistidyl, R′—R″ = —CH_2—CH_2—CH_2—
(2a), R = leucylalanyl, R′ = R″ = H
(2b), R = pyroglutamylhistidyl, R′—R″ = —CH_2—CH_2—CH_2—

The model peptide leucylalanylglycine amide and the thyrotropin-releasing factor (TRF), pyro-L-glutamyl-L-histidyl-L-proline amide (L-5-oxo-2-pyrrolidinylcarbonyl-L-histidyl-L-prolinamide)[8,9] were synthesized, in order to test the utility of this novel route to peptide amides.

Boc-glycyldehydroalanine (Boc = *tert*-butyloxycarbonyl) [m. p. 157–159 °C, decomp., $\lambda_{max}(CH_3OH) = 241$ nm ($\varepsilon = 5560$); Gly 1.00; NH_3 1.03], prepared in 84 % yield from Boc-glycyl-*O*-tosylserine methyl ester by β-elimination[10], was coupled to the chloromethylated (1.25 mmol Cl/g) styrene-2 % divinylbenzene copolymer[4] in dimethylformamide in the presence of triethylamine (40 °C; 48 h) to give the peptide resin *(1a)* (0.41 mmol Boc-dipeptide/g).

Boc-leucylalanylglycyldehydroalanine resin *(1b)* was obtained after two successive cycles of solid phase synthesis[4,11] with Boc-amino acids under the reaction conditions given in Table 1. Treatment of *(1b)* in the presence of 1 equivalent of water with 1 N hydrogen chloride in glacial acetic acid for 30 min at 50 °C resulted in a) the cleavage of the dehydroalanine residue with formation of the amide *(2a)* and the pyruvyl resin *(3)*; b) the simultaneous removal of the Boc-protecting group from the H_2N-terminus.

Leucylalanylglycine amide *(2a)* was solidified by trituration in ethyl ether. Crystallization from methanol/ethyl ether gave a product (91 % yield) which showed single spots and the given R_f values upon thin layer chromatography on silica gel in the following solvent systems[12]: A 0.14, B 0.62, C 0.35; Gly 1.00, Ala 0.98, Leu 1.00, NH_3 0.98. Elemental analysis gave the expected values.

Table 1. Solid phase synthesis of peptides attached to the support *via* dehydroalanine. Boc-amino acids and DCC were used in fivefold excess. Abbreviations: TFA = trifluoroacetic acid; NEt_3 = triethyl amine; Boc = *tert*-butyloxycarbonyl; DCC = dicyclohexylcarbodiimide; AA = amino acid.

Synthesis Step	Time [min]
1. CH_2Cl_2 wash (4 ×)	1.5
2. 25 % TFA—CH_2Cl_2 prewash (1 ×)	1.5
3. 25 % TFA—CH_2Cl_2 deprotection (1 ×)	30.0
4. CH_2Cl_2 wash (5 ×)	1.5
5. 10 % NEt_3—CH_2Cl_2 prewash (1 ×)	1.5
6. 10 % NEt_3—CH_2Cl_2 neutralization (1 ×)	10.0
7. CH_2Cl_2 wash (5 ×)	1.5
8. Boc—AA—CH_2Cl_2 (1 ×)	10.0
9. DCC—CH_2Cl_2 (1 ×)	180.0
10. CH_2Cl_2 wash (3 ×)	1.5
11. EtOH wash (3 ×)	1.5

Boc-prolyldehydroalanine [m. p. 154–156 °C; $\lambda_{max}(CH_3OH) = 240$ nm ($\varepsilon = 5300$); Pro 1.00, NH_3 1.01], obtained in 59 % yield from Boc-prolyl-*O*-tosylserine methyl ester under the conditions of β-elimination[10], was coupled (25 °C; 48 h) to the chloromethylated (2.3 mmol Cl/g) styrene-2 % divinylbenzene copolymer as described for *(1a)* to give the Boc-prolyldehydroalanine resin *(1c)* (0.51 mmol of Boc-dipeptide/g).

Boc-pyroglutamylhistidylprolyldehydroalanine resin *(1d)* was synthesized according to the procedure given for *(1b)* using Boc-amino acids in the coupling steps.

Pyroglutamylhistidylproline amide (TRF) *(2b)* was isolated after treatment of *(1d)* with 1 equivalent of water in 1 N hydrogen chloride in glacial acetic acid as specified for *(2a)*. A minor contamination was removed by partition chromatography on silica gel in the solvent system chloroform/methanol = 1:1. The purified tripeptide amide (TRF) gave single spots and the given R_f values upon thin layer chromatography in the following solvent systems[12]: A 0.03, B 0.46, D 0.27, E 0.27; Glu 1.00, Pro 1.02, His 0.99, NH_3 1.00; $[\alpha]_D^{20} = -45.1$ (*c* 0.25 glacial acetic acid); yield 63 %.

The biological activities of *(2b)* and another sample of synthetic[13] TRF (Abbott Laboratories, North Chicago, Illinois) were compared in the mouse bioassay[14,15]. Potency estimates and 95 % confidence limits (C. L.) were calculated by the methods of *Brownlee*[16] and *Finney*[17], respectively. One nanogram of TRF synthesized on the dehydroalanine resin was equivalent to 1.2 nanograms (95 % C. L. 0.67–2.20 ng) of the reference preparation.

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[**] Solid Phase Syntheses with α,β-Unsaturated Amino Acids, Part I.

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Statistical Synthesis and Intraannular Reaction of a Rotaxane[**][1]

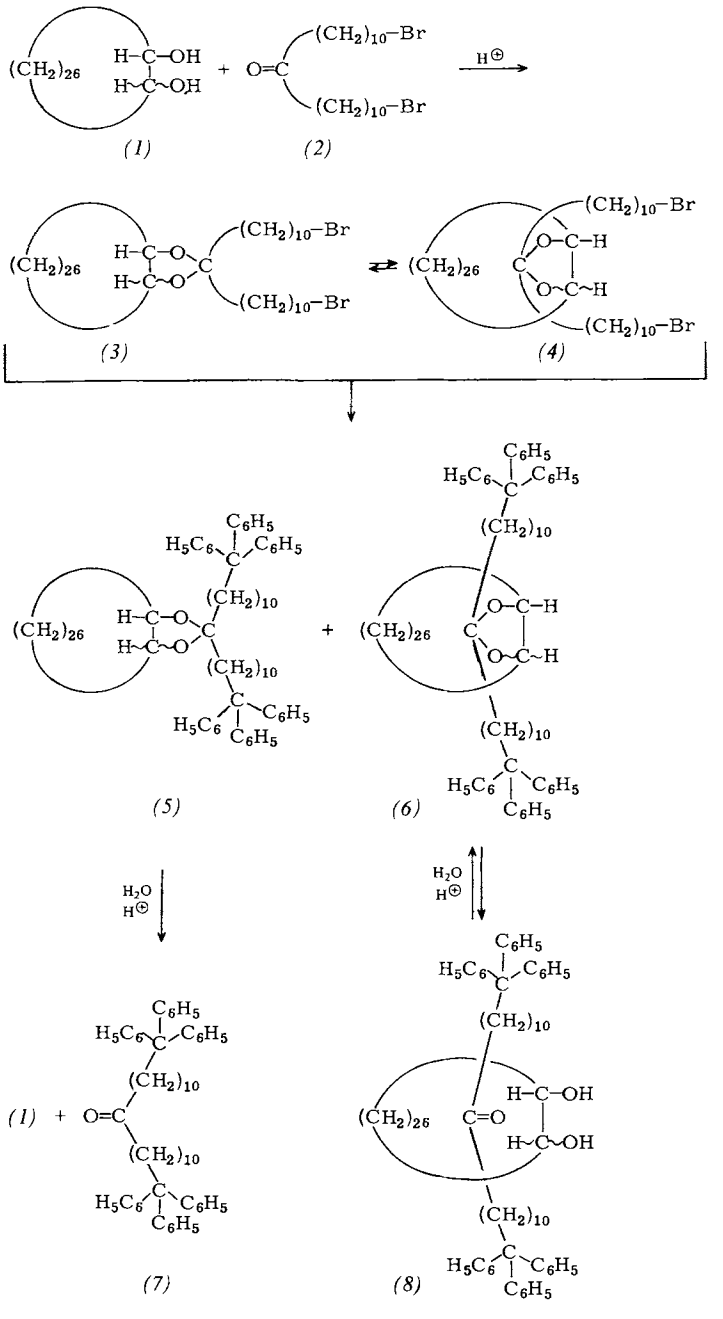
By *Gottfried Schill, Wolfgang Beckmann*, and *Walter Vetter*[*]

So far, only two variants of the statistical syntheses of rotaxanes[2] have been realized[3]. Described here is the statistical synthesis of the rotaxane *(8)* starting from the 28-membered macrocyclic diol *(1)* and the long-chain α,ω-bifunctional ketone *(2)*.

The ketalization of *(1)* (mixture of meso- and racemic forms) with *(2)* in the presence of *p*-toluenesulfonic acid[4] gave the ketal *(3)*, which might exist in extra-intraannular conformational equilibrium with *(4)*. The mixture obtained was converted into *(5)* and the prerotaxane *(6)* by reaction with triphenylmethyllithium[5] at −15 to −20 °C. Acid-catalyzed hydrolysis of the mixture gave the starting diol *(1)*, the axis *(7)*, and the rotaxane *(8)*. Separation by column and thin-layer chromatography afforded the rotaxane *(8)* as a colorless oil [yield: 0.12% based on *(5)* + *(6)*]. In a second experiment the yield amounted to 0.13%. In all solvents used so far it appears as a single spot in the thin-layer chromatogram.

The rotaxane *(8)* was characterized by its mass, NMR, and IR spectra.

In the mass spectrum the peak for the trityl ion is so intense, *m/e* 243 (100%) (no other peak, apart from those of its isotopic and fragmentation ions *m/e* 165 (5%) and 167 (5%) reach a height of 4% of the base peak), that only a few peaks of relatively slight intensity can be ascribed to the rotaxane structure of the molecule.



The molecular ion M^+ (*m/e* 1218) is scarcely detectable. The upper end of the spectrum terminates with a series of peaks at *m/e* 1214 to 1218 (0.005% of the base peak) due to M and (M − H) peaks of dehydrogenation products, as are often observed for large molecules with extensive fragmentation. Characteristic mass peaks occur at *m/e* 1200 (0.05%) and 1182 (0.10%). These correspond to the loss of one and two molecules of water, respectively, from the rotaxane molecular ion[6]. The mass range below these signals is devoid of peaks down to *m/e* 795. The ion *m/e* 795 (0.48%) corresponds to the protonated axial moiety and constitutes a fragment typical of all mechanically linked molecules[2]. It is formed by transfer of a hydrogen atom from the ring to the axis within the same molecule. The radical center on the ring thus formed can lead to fragmentation of the ring and thus to release of the axis. The protonated axis exhibits a characteristic cationic fragmentation: it eliminates two molecules of benzene in two steps, thus giving rise to two mass peaks at *m/e* 717 (2.2%) and 639 (0.45%).

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These are accompanied by two extraordinarily intense signals of the corresponding metastable ions.

The diol *(1)* is characterized by mass peaks at *m/e* 423 (M−H, 0.15%) and 407 (M+H−H_2O, 0.34%). The appearance of these ions is typical for the fragmentation of protonated alcohols, as observed after chemical ionization[7], and is indicative of an H-transfer from the axis to the ring.

^{1}H-NMR spectrum in CCl_4 (100 MHz, TMS internal): δ = 7.16 (m, 30 Aryl-H), 4.30 (t, 2 H—C—O), 2.48 (t, 4 CH_2-trityl), 2.30 (t, 4 CH_2—CO), 1.47 (s, 2 OH), 1.26 ppm (m, 84 CH_2).

IR spectrum (film): 3400 (OH), 1710 cm^{-1} (C=O).

The prerotaxane *(6)* was obtained in pure form as a colorless oil (yield 55%) by reketalization of *(8)* with *p*-toluenesulfonic acid in the presence of a 5 Å[8] molecular sieve. It was characterized by its mass spectrum [*m/e* 1200, 0.17% (M^+), 817,52% (M−trityldecyl), 243, 100% (trityl)].

The synthesis of *(6)* from *(8)* is the first example of an intraannular[9] reaction.

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$Te_3Cl_{13}^-$: A Novel Ionic Degradation Product of the Cubane-Type Compound $(TeCl_4)_4$[**]

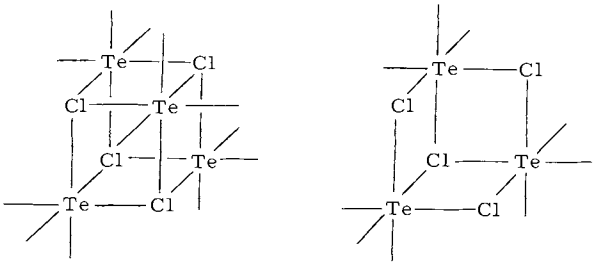
By *Bernt Krebs* and *Volker Paulat*[*]

Depending on the electronic environment, the stereochemical activity of the inert electron pair on the Te atom in tellurium(IV) halides leads to various and, in some cases, unusual types of structures: Thus, the adduct $TeCl_4 \cdot AlCl_3$[1,2] contains $TeCl_3^+$ and $AlCl_4^-$ ions and in $TeCl_4 \cdot PCl_5$[3,4] polymeric $(TeCl_5^-)_n$ and PCl_4^+ ions are present, while tellurium tetrachloride itself has a tetrameric, cubane-type molecular structure in the solid state[5].

Molecular weight determinations on benzene solutions of $TeCl_4$[6,7] indicated the probability of equilibria between $(TeCl_4)_4$ and lower molecular species. We therefore attempted to isolate possible degradation products of $(TeCl_4)_4$ from such solutions: When a solution of equimolar amounts of tellurium(IV) chloride (Te_4Cl_{16}) and triphenylmethyl chloride (or chlorides of other large organic cations such as, *e.g.* $(C_2H_5)_4N^+$, cf. Ref. [8]) in benzene is warmed gently, a dark brown solution is formed from which yellow-brown needle-shaped crystals having the composition $(C_6H_5)_3CTe_3Cl_{13}$ can be isolated:

$$Te_4Cl_{16} + (C_6H_5)_3CCl \rightarrow (C_6H_5)_3CTe_3Cl_{13} + 1/4\ Te_4Cl_{16}$$

The compound is stable at room temperature in absence of moisture and melts at 196—198 °C. As shown by complete X-ray structural analysis, the novel $Te_3Cl_{13}^-$ ion is in fact structurally a fragment of $(TeCl_4)_4$, from which a $TeCl_3^+$ group has been cleaved by a Cl^- ion functioning as Lewis base:



Te_4Cl_{16} $Te_3Cl_{13}^-$

The $Te_3Cl_{13}^-$ ion consists of three distorted $TeCl_6$ octahedra, joined *via* edges to give a trigonal unit with idealized C_{3v} symmetry. This general type of $x_3\ y_{13}$ structure has been predicted from structural systematics, but it has not been observed previously.

The bond lengths and mean bond angles are given in Figure 1. Similarly as in $(TeCl_4)_4$, in $TeCl_3^+AlCl_4^-$ and $PCl_4^+TeCl_5^-$ the difference between terminal bond lengths (mean value 2.342 Å) and bridge bond lengths (mean value 2.841 Å) is considerable because of presence of the inert electron pair and as a result of the weaker bridging bonds; as expected the bonds to the triply bound bridge atom Cl-1 are the longest.

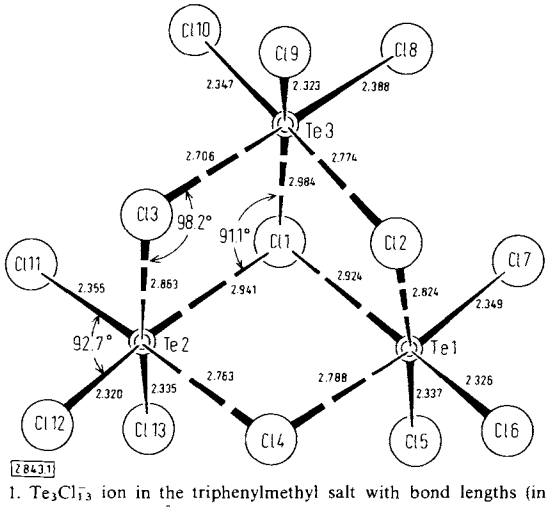


Fig. 1. $Te_3Cl_{13}^-$ ion in the triphenylmethyl salt with bond lengths (in Å, standard error 0.005 Å) and bond angles (averaged over chemically equivalent angles).

$(C_6H_5)_3CTe_3Cl_{13}$ crystallizes monoclinically ($P2_1/c$) with $a = 11.095$, $b = 16.444$, $c = 20.439$ Å; $\beta = 114.50°$; $Z = 4$; $d_{x\text{-ray}} = 2.13$, $d_{exp} = 2.12$ g cm^{-3}.

The IR spectrum (Nujol/polyethylene) shows bands in the 400—33 cm^{-1} range at 341, 332, 317, 305, 208, 170, 156, 72 cm^{-1}, the first four being mainly due to the vibrations of the terminal $TeCl_3$ groupings.

If the above degradation of tetrameric tellurium(IV) chloride is carried out a stage further (cf. also Ref. [8, 9]), using 2 mol

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of chloride donor per mol Te_4Cl_{16}, a further $TeCl_3^+$ group is split off to give compounds of the type $M^I_2Te_2Cl_{10}$ (M^I voluminous cation). When using tetraphenylarsonium chloride the compound $[(C_6H_5)_4As]_2Te_2Cl_{10}$ could be isolated as yellow crystalline platelets in analytically pure form.

The new $Te_2Cl_{10}^{2-}$ ion, whose dimeric structure has been confirmed by cryoscopic measurements, very probably consists of two edge-to-edge coupled octahedra. A structural analysis is under way. $[(C_6H_5)_4As]_2Te_2Cl_{10}$ crystallizes triclinically ($P\bar{1}$) with $a=12.114$, $b=20.663$, $c=10.654$ Å; $\alpha=94.44$, $\beta=94.07$, $\gamma=89.73°$; $Z=2$; $d_{x\text{-ray}}=1.72$, $d_{exp}=1.70\,g\,cm^{-3}$.

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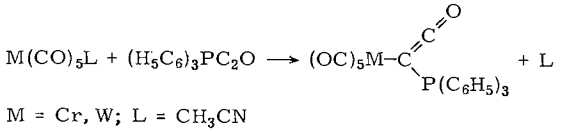
Phosphorus Ylide Complexes of Group VI as Sources of Carbonylmethylene[**]

By *Heinz Berke* and *Ekkehard Lindner*[*]

Because of their lability phosphorus ylide complexes[1-5] can undergo interesting rearrangements. We have observed that, apparently because of the reduced basicity of the resonance-stabilized ylide, Wittig-like reactions do not occur when (carbonylmethylene)triphenylphosphorane[6] reacts with hexacarbonyl complexes of group VI metals[2,4]; instead, ylide complexes are formed by replacement of CO. For chromium and tungsten it is preparatively best to use the photochemically produced complexes $M(CO)_5CH_3CN$[7]:



$M(CO)_5L + (H_5C_6)_3PC_2O \longrightarrow (OC)_5M{-}C(=C{=}O)P(C_6H_5)_3 + L$

M = Cr, W; L = CH_3CN
M = Mo; L = CO

M	Cr	Mo	W
	(1)	*(2)*	*(3)*
m.p. (dec.) [°C]	146	105	145

Elemental analyses, molecular weight determinations and IR and mass spectra proved the composition and structure of the new ylide complexes *(1)*—*(3)*; these are yellow and in some cases soluble even in nonpolar solvents.

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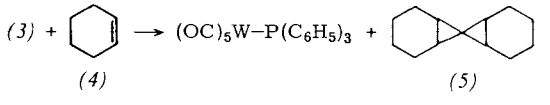
Table 1. Characteristic IR frequencies (in cm^{-1}) of the ylide complexes *(1)*—*(3)*.

Compound	ν(CO)	$\nu_{as}(C_2O)$	$\nu_s(C_2O)$	Phase
$(H_5C_6)_3PC_2O$		2104 vs	1312 m	Solid/KBr
		2104 vs		Soln./CCl_4
(1)	2051 s (A_1)	2083 s		
	1977 vw (B_1)			
	1932 vs (E)			
	1904 s (A_1)			
			1310 m	Solid/KBr
(2)	2061 m-s (A_1)	2084 m-s		Soln./CCl_4
	1985 w (B_1)			
	1938 vs (E)			
	1906 s (A_1)			
			1314 m	Solid/KBr
(3)	2058 m-s (A_1)	2084 m-s		Soln./CCl_4
	1953 w (B_1)			
	1928 vs (E)			
	1903 s (A_1)			
			1311 w	Solid/KBr

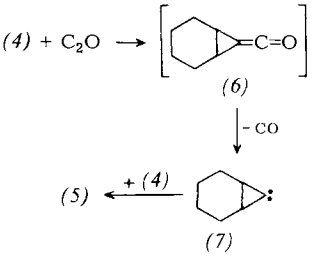
The C_2O group of (carbonylmethylene)triphenylphosphorane is characterized especially by the asymmetric and symmetric C_2O stretching vibrations (see Table 1). On coordination of the ligand to chromium, molybdenum or tungsten $\nu_{as}(C_2O)$ is shifted by *ca.* 20 cm^{-1} towards lower frequencies. The long-wave position of the CO stretching vibrations of the $M(CO)_5$ groups of *(1)*—*(3)* indicates that, as expected, the ylide ligand has only slight π-acceptor character. Its easy replacement by tetrahydrofuran or dimethylformamide is to be ascribed to the same cause, as shown by time-dependent IR studies. In only slightly polar solvents such as CCl_4 the compounds *(1)* and *(2)* yield $Cr(CO)_6$ and $Mo(CO)_6$, respectively, along with unidentified products; with the more stable tungsten complex *(3)* an analogous result is observed only above 50 °C. Further, the mass spectra, which are characterized by thermolysis reactions, display rearrangements of this type.

It should be particularly noted that $M(CO)_5P(C_6H_5)_3$ (M = Cr, Mo or W) and C_2O occur as products of thermolysis. If the tungsten complex *(3)* is heated with a carbene trapping substance, *e.g.* cyclohexene *(4)*, for some hours at 110 °C, analytically pure $W(CO)_5P(C_6H_5)_3$ can be isolated [ν(CO): 2073 m, 1985 w, 1945 vs cm^{-1}; solution in CCl_4]; 7,7'-spirobinorcarane *(5)*[8] can also be obtained on thin-layer chromatography.



(3) + *(4)* → $(OC)_5W{-}P(C_6H_5)_3$ + *(5)*

Formation of *(5)* is indicated particularly by the mass spectrum: molecular ion at $m/e=176$; olefinic ν(C—H) and ν(C=C) absorptions do not appear in the IR spectrum, but only more aliphatic C—H and C—C stretching vibrations. *(5)* is probably formed from the carbene C_2O and



(4)[9] by way of an unstable cyclohexyleneketene *(6)* which is converted by spontaneous loss of CO into the carbene *(7)* which reacts further with an excess of *(4)*.

Experimental:

$M(CO)_5CH_3CN$ (M = Cr or W) (3 mmol) is heated with $(C_6H_5)_3PC_2O$ (906 mg, 3 mmol) in boiling diethyl ether (50 ml) for 3—4 h under N_2. The mixture is filtered and the residue is extracted with ether. After removal of the ether from the solution, chromatography in benzene on an Al_2O_3 column (activity III) under N_2 gives an eluate which is concentrated under reduced pressure. Treatment with light petroleum in excess at −30 °C yields needles of the ylide complex *(1)* or *(3)*, which after isolation are dried in vacuum (yield 20—30%). For preparation of the molybdenum compound *(2)*, $Mo(CO)_6$ (2.64 g, 10 mmol) and $(C_6H_5)_3PC_2O$ (3.02 g, 10 mmol) are heated in benzene (50 ml) under N_2 for 4 h at 80 °C; after removal of the solvent the excess of $Mo(CO)_6$ is sublimed off in high vacuum and the product is purified as for *(1)* and *(3)*.

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^{13}C-NMR Spectrum of Ketene[**]

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^{13}C-NMR spectroscopy can provide insights into the bonding situation and electron distribution of the ground state of organic molecules through the chemical shifts and spin-spin coupling constants[1,2] if sufficiently similar molecules are compared.

In connection with a systematic investigation of the molecular structure of allenes[3], and ketenes[4] we have measured the ^{13}C spectra of a series of ketene derivatives[4]. Ketene itself shows unusual resonance positions, not only in comparison with those of the isoconjugated allene but also with the chemical shifts of organic compounds in general. The proton noise decoupled PFT ^{13}C-NMR spectrum was measured at 22.63 MHz in $CDCl_3$, with TMS as internal standard, at −60 ± 5 °C on a Bruker-HX-90 spectrometer. The chemical shifts δ_C and the ^{13}C—H spin-spin coupling constant we have found are given in Figure 1.

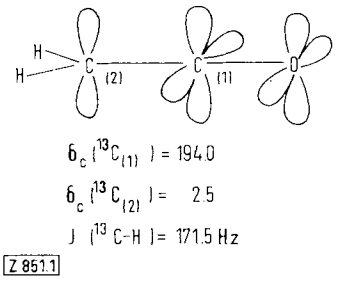
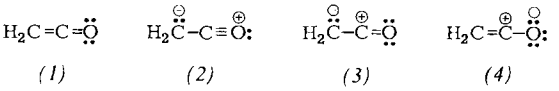


Fig. 1. ^{13}C-NMR data of ketene. Chemical shifts [ppm] referred to TMS.

The most remarkable characteristic of the ketene spectrum is the extreme high-field position of the terminal carbon atom resonance—far outside the region usually assumed to be typical for formally sp^2-hybridized carbon atoms: the terminal carbon atom is shielded by about 120 ppm relative to ethylene (δ_C = 122.8 ppm)[2]. Even with respect to the terminal carbon atom resonance of allene (δ_C = 74 ppm)[2], where this carbon is also bonded to a formally sp-hybridized carbon atom, a high-field shift of 72 ppm is found. The terminal C atom of ketene is even one of the most shielded carbon atoms so far observed in ^{13}C-NMR spectra of organic compounds[2]; its chemical shift is less than that of ethane (δ_C = 5.9 ppm)[2].

Calculations of the shielding constants with CNDO orbitals[4] indicate that the stronger shielding of the terminal carbon atom of ketene in comparison to that in allene has to be attributed to both a larger diamagnetic and a less negative paramagnetic shielding constant resulting from higher electron density at that atom. On the other hand, the ^{13}C—H spin-spin coupling constants of ketene (Fig. 1) and allene [$J(^{13}C—H)$ = 168 Hz][2] are of comparable magnitude. The value of the ^{13}C—H coupling constant is mainly determined by the Fermi contact term, which depends upon the size of the valence s-orbitals thus reflecting the hybridization. The almost identical values of $J(^{13}C—H)$ for these two molecules therefore indicate that their σ-bonding situation is very similar and that the stronger shielding in ketene has to be attributed mainly to a higher π-electron density.

The central C atom in ketene is strongly deshielded, as is that in allene (δ_C = 213 ppm)[2]. Compared with the resonance position of carbon monoxide $:\overset{\ominus}{C}\equiv\overset{\oplus}{O}:$ (δ_C = 181.3 ppm)[2], the central C atom resonance in ketene is shifted somewhat to lower field and is found in the region of carbonylmetal complexes, *e.g.* $Ni(CO)_4$ (δ_C = 191.6 ppm)[2]. This result shows the considerable triple-bond character of the C=O bond of ketene and is in agreement with a MO description of ketene with localized CNDO orbitals[5]. According to this picture, ketene has two sets of π-orbitals, one being delocalized over two centers, and the other over three centers, from O to C-2 (Fig. 1). The latter is therefore isoconjugated with the π-system of an allyl anion.



(1) *(2)* *(3)* *(4)*

As the result, ^{13}C-NMR spectroscopic data show that of the mesomeric structures of ketene *(1)*—*(4)*, the structure *(2)* contributes significantly to the ground state. This is in agreement with the molecular *g* value and the para-

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magnetic susceptibility along the C—C—O bond axis according to which the C—O bond must have an almost cylindrical symmetry[6].

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Asymmetric Induction by a Chiral Bisphosphane-Rhodium Complex in the Hydroformylation of Aliphatic Olefins[1]

By *Giambattista Consiglio, Carlo Botteghi, Christian Salomon*, and *Piero Pino*[*]

We have already reported on the asymmetric hydroformylation of aromatic olefins with chiral cobalt- and rhodium-complexes as catalysts[1]. In the present communication we now describe the hydroformylation of aliphatic olefins in presence of catalysts prepared *in situ* from (−)-2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)-butane["(−)-diop"] and $RhH(CO)(PPh_3)_3$. Hydroformylations carried out by the usual methods[2] gave the results shown in Table 1, which we interpret as follows:

1. Asymmetric induction is greater at room temperature and normal pressure than under "typical oxo conditions"[3]. The reaction conditions, however, do not appear to have any influence on the prevailing configuration of the products. The highest optical yield (27%) was achieved in the case of *cis*-butene.

2. The (*R*) enantiomer predominates in all the aldehydes formed from vinyl olefins.

3. The optical purity of the aldehydes generated from *cis*-olefins is greater than that of the aldehydes arising from the corresponding *trans*-olefins; their prevailing configurations, however, are identical.

4. The prevailing configuration of the 2-methylbutanal obtained from 1-butene is different from that of the same aldehyde obtained from *cis*- and *trans*-butene.

5. The two aldehydes obtained from *cis*- and *trans*-2-hexene, 2-methylhexanal and 2-ethylpentanal, have different prevailing configurations.

Formally, the predominating enantiomer of the aldehyde, in the case of prochiral[4] olefin formylation, is always formed by addition of carbon monoxide and hydrogen to the same "prochiral side" of the olefin, *i.e.* that side of the olefin which, when bound to the metal atom, generates the (*S*) configuration at the carbon atom undergoing the attack by carbon monoxide (scheme (1))[5].

Since the 2-methylbutanal obtained from *trans*-butene has a different prevailing configuration from that obtained from 1-butene, the two diastereomeric alkylrhodium complexes [scheme (2): *(3a)* and *(3b)*], which can be considered as intermediate products[2], must be formed in different concentrations. As a consequence the in asymmetric induction takes place during the formation of the alkylrhodium complex, *i.e.* during the formation of the π complexes *(2a)* and *(2b)* and/or their transformation into *(3a)* and *(3b)*. As yet, it is not possible to decide whether this asymmetric induction determines which aldehyde antipode will predominate in the reaction products, as a possible asymmetric induction during subsequent reaction steps[2], namely during the reversible CO insertion and the aldehyde splitting, could reverse the prevailing arrangement of the alkyl groups around the asymmetric carbon atom.

It is remarkable that olefins having symmetry C_{2v} (with a plane of symmetry perpendicular to the double bond)

Table 1. Hydroformylation of aliphatic olefins with $RhH(CO)(PPh_3)_3$ and (−)-diop (molar ratio 1:4) in aromatic solvents [olefin/rhodium = 3.0×10^2 – 1.6×10^3; $p_{H_2}/p_{CO} = 1$].

Olefin	$p_{H_2}+p_{CO}$ [atm]	T [°C]	Product ratio linear/branched	Optically active compound isolated			
				Name	$[\alpha]_D^{25}$ (l = 1) (neat)	Configuration	Optical purity [%]
1-Butene	0.67 [a]	25	12.6	2-Methylbutanal	−5.27	*R*	18.8 [7]
1-Pentene	1	25	13.5	2-Methylpentanoic acid [c]	−3.62 [d]	*R*	19.7 [8]
3-Methyl-1-butene	1	25	13.3 [b]	2,3-Dimethylbutanal	−4.38 [e]	*R*	15.2 [9]
1-Octene	1	25	8.8	2-Methyloctanal	−4.91	*R*	16.5 [g]
cis-Butene	0.67 [a]	20	only branched [f]	2-Methylbutanal	+7.57	*S*	27.0
cis-Butene	84	95	only branched	2-Methylbutanal	+2.28	*S*	8.1
cis-Butene [i]	86	95	only branched	2-Methylbutanal	+2.22	*S*	7.9
trans-Butene	84	98	only branched	2-Methylbutanal	+0.89	*S*	3.2
cis-2-Hexene	82	95	1.5 [h]	2-Methylhexanoic acid [c]	+1.68	*S*	7.6 [10]
				2-Ethylpentanoic acid [c]	−0.22	*R*	5.8 [11]
trans-2-Hexene	82	95	1.4 [h]	2-Methylhexanoic acid [c]	+0.31	*S*	1.4
				2-Ethylpentanoic acid [c]	−0.11	*R*	2.9

[a] Partial pressure of the gaseous olefin 0.33 atm.
[b] Ratio 4-methylpentanal/2,3-dimethylbutanal.
[c] Oxidation with Ag_2O [12].
[d] Extrapolated from a 7% solution in hexanoic acid.
[e] Extrapolated from a 2% solution in 4-methylpentanal.
[f] The *n*-pentanal (≈ 5%) probably arises from 1-butene as contaminant in the 2-butene.
[g] Determined by conversion into (+)-(*S*)-3-methylnonane ($[M]_D^{25}$ (max) = +14.0 [13]).
[h] Ratio 2-methylhexanal/2-ethylpentanal.
[i] Rh_2O_3 was used instead of $RhH(CO)(PPh_3)_3$.

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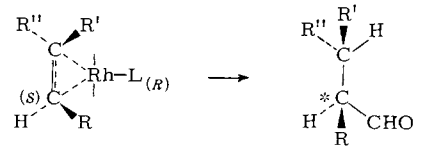
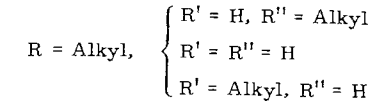
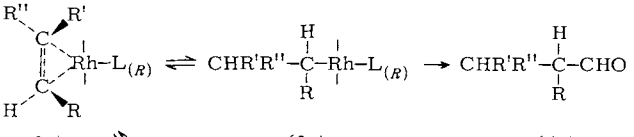


(1)





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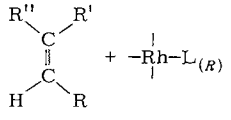
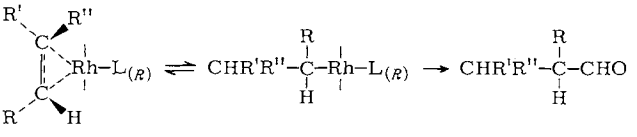


(2)

(1)



(2b) (3b) (4b)

such as *e.g. cis*-butene are asymmetrically hydroformylated. Since both sides of the olefin are equivalent in this case, the alkylrhodium diastereomers should be formed in equal concentration and the asymmetric induction should take place in later reaction steps. However, the possibility that the asymmetric induction for this olefin takes place partly or exclusively during formation of the alkylrhodium complex should not be overlooked. In fact, due to the presence of the asymmetric ligand in the catalytic complex, the olefin could have a preferred conformation, and thus the reactivities of the two olefinic asymmetric carbon atoms bound to the metal atom could be different.

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Tetraiodosilanebis[tricarbonyliron(0)] [**]

By *Günter Schmid*[*] and *Hans-Peter Kempny*

The halogen atoms of neutral inorganic halides form potential complex ligands. We describe here the first example of coordination of such "Lewis bases" to metal atoms of carbonyl-metal compounds.

The synthesis of tetraiodosilanebis[tricarbonyliron(0)] *(1)* confirms that such complexes are capable of existence. After UV irradiation of a solution containing a mixture of $Fe(CO)_5$ and SiI_4 in molar ratio 5:1 in pentane, a complex $SiI_4[Fe(CO)_3]_2$ is formed which can be isolated, although in very small yield, as volatile, dark red crystals. This new complex is readily soluble in apolar solvents such as cyclohexane, pentane, benzene, *etc.* It decomposes rapidly above 35 °C, even under an inert gas; light and air also cause decomposition; however, the compound can be sublimed at 20 °C/0.1 torr and is stable for a considerable time below −15 °C. Osmometric molecular weight determination shows the compound to exist as the monomer (exp. 798; calc. 815.5).

That $SiI_4[Fe(CO)_3]_2$ is considerably more volatile than SiI_4 is presumably due to shielding of the coordination sphere of the tetrahedral SiI_4 molecule by the $Fe(CO)_5$ units since this hinders intermolecular interaction between the I and the Si atoms in the crystal lattice.

The IR spectrum of *(1)* shows four CO stretching vibrations, at 2076, 2045, 2010 and 2002 cm^{-1}, of which two result from splitting of the longest-wave band. Only the decoupled $Fe(CO)_3$ groups should be subject to the selection rules for the symmetry of these vibrations, since coupling of the ν(CO) vibrations *via* SiI_4 can be ruled out[11].

Assuming a trigonal-bipyramidal environment for both iron atoms a pair of three CO stretching vibrations should be observed in the *cis*-configuration (Fig. 1) for both C_{2v} and C_s symmetry[2]. D_{3h} symmetry with *trans*-I ligands can be excluded for steric reasons; it permits only one IR-active CO stretching vibration. Splitting of the longest-wave ν(CO) vibration is presumably due to a small decrease in the symmetry of the $Fe(CO)_3$ group[3].

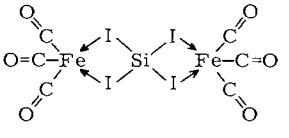

Fig. 1. Proposed structure of $SiI_4[Fe(CO)_3]_2$ *(1)*.

The occurrence of unchanged tetraiodosilane in the complex can be proved by reaction of *(1)* with tributylphosphane or pyridine, which affords $SiI_4 \cdot P(C_4H_9)_3$ or $SiI_4 \cdot 4C_5H_5N$[4], respectively.

Experimental:

A solution of SiI_4 (5.36 g, 10.0 mmol) and $Fe(CO)_5$ (9.80 g, 50.0 mmol) in pentane (400 ml) is irradiated with rigorous exclusion of air in a water-cooled recycling apparatus by a 150 W UV lamp for 4—5 h. The solution rapidly turns brown and CO is evolved. After filtration, the reaction

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mixture is freed from solvent and the excess of $Fe(CO)_5$ under reduced pressure at 0—10 °C. A carmine-red oil can be separated from the residue in a high vacuum and this eventually crystallizes. Further purification by sublimation in a high vacuum at room temperature affords 10—20 mg of dark red crystals of composition $SiI_4[Fe(CO)_3]_2$.

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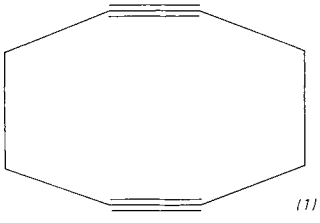
1,5-Cyclooctadiyne[***]

By *Else Kloster-Jensen* and *Jakob Wirz*[*]

In the course of our investigations on butatriene we have isolated small quantities of the highly strained, hitherto unknown compound, 1,5-cyclooctadiyne *(1)*. It crystallizes in colorless prisms, dec. 105 °C, which are stable at 0 °C under exclusion of air.



(1)

Z 854.1

The monocyclic hydrocarbon *(1)* is characterized by the following spectroscopic data: ^{1}H-NMR: one singlet at $\delta = 2.62$ ($CDCl_3$/TMS), 2.53 (CCl_4/TMS), 2.21 ppm (C_6D_6/TMS). ^{13}C-NMR (C_6D_6): δ (referred to TMS) = 20.2 (t, $J_{CH} \approx 140$ Hz), 95.8 ppm (s). MS: $m/e = 104.0611 \pm 0.002$ (calc. 104.0626), 103, 78, 52; $m^* = 58.5$ for $104 \rightarrow 78 + 26$. IR (CCl_4): 2910, 2865, 2832, 2237 (weak), 2175 (weak), 1436, 1423, 1115, 552, 434 cm^{-1}. UV (*n*-pentane): end-absorption $\lambda < 230$ nm. Photoelectron spectrum: three superimposed π-bands in the range of 9.0 to 10.0 eV, a fourth π-band at 10.1 eV.

Catalytic hydrogenation of *(1)* yields cyclooctane almost quantitatively after uptake of four equivalents of H_2. Ozonolysis of *(1)*, followed by alkaline hydrolysis, affords succinic acid in good yield as sole product. Conclusive evidence for the structure of *(1)* was provided by an X-ray structure analysis by *Römming*[1]. The molecule has a center of symmetry, and the carbon ring deviates only slightly from planarity (0.023 Å from the regression plane through the C-atoms). Interatomic distances: C1—C2 1.185, C2—C3 1.459, C3—C4 1.530, and C1—C6 2.569 Å. Bond angles: $\sphericalangle$ C1—C2—C3 159.1 and $\sphericalangle$ C2—C3—C4 110.8° (standard deviations ≤ 0.005 Å and 0.3°).

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[1] Preliminary data from Dr. *Chr. Römming,* private communication.

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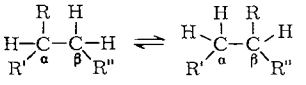
Stereochemistry of the Coenzyme-B_{12}-dependent Methylmalonyl-CoA-Mutase Reaction. Investigation with Ethylmalonyl-CoA[**]

By *János Rétey* and *Boleslaw Zagalak*[*]

All the coenzyme-B_{12}-dependent enzymatic rearrangements studied so far proceed according to eq. (1):



(1)

The replacement of R by H or of H by R occurring at C_α and C_β has been investigated stereochemically in a few cases, but in none of these cases could the steric course be elucidated at both migration centers. Inversion was observed in the glutamate-mutase reaction ($R = CHNH_2$—COOH, $R' = COOH$, $R'' = H$)[1] and in the propanedioldehydrase reaction ($R = R'' = OH$, $R' = CH_3$)[2], and retention in the methylmalonyl-CoA-mutase reaction ($R = COSCoA$, $R' = COOH$, $R'' = H$) at the center studied[3].

The difference in the steric course was remarkable because of the analogies previously observed between these reactions[4]. Is the mechanism of the methylmalonyl-CoA-mutase reaction really different from that of the other two rearrangements or is the steric course not an immediate consequence of the mechanism of the rearrangement step? To answer this question it was desirable to study the steric events if possible at both migration termini in the methylmalonyl-CoA-mutase reaction. Methylmalonyl-CoA itself is not suitable for such a study. On the other hand we found that ethylmalonyl-CoA is also a substrate for the mutase from *Propionibacterium shermanii*.

We have treated (2*RS*)-ethylmalonyl-CoA, prepared analogously to (2*RS*)-methylmalonyl-CoA[5], with purified me-

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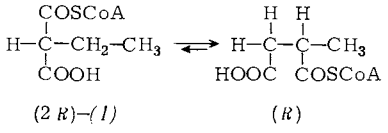
thylmalonyl-CoA-mutase from *Propionibacterium shermanii*[6]. The reaction was about 1000 times slower than that of the natural substrate, as was shown by gas-chromatography of the product mixture after its conversion into the dimethyl ester. Simultaneous mass-spectroscopic investigation proved that the product was indeed a mixture of dimethyl ethylmalonate and methylsuccinate. After hydrolysis, the main portion of the product mixture was separated by thin-layer chromatography and the methylsuccinic acid was assigned (*R*)-chirality on the basis of its ORD spectrum[7]. On the well-founded assumption that the ethylmalonyl-CoA *(1)* taking part in the mutase reaction has the same configuration [(2*R*)] as the natural substrate[3,8], the enzymatic reaction can be described by eq. (2):



(2)

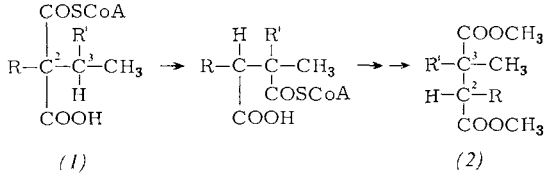
(2*R*)-*(1)* (*R*)

To obtain further information about the steric course of the reaction, specifically deuterated substrates were introduced. Dimethyl methylsuccinate seemed a suitable derivative for differentiation of the methine and methylene protons in the product: its corresponding protons appear in the 220 MHz NMR spectrum as three separate multiplets [($CDCl_3$), $\delta = 2.35$ (q), 2.70 (q), and 2.90 (sex)]. Assignment of the methylene protons to the two quadruplets at 2.35 and 2.70 ppm was achieved by means of the spectra of stereospecifically deuterated reference samples. Treating methylfumaric (mesaconic) or methylmaleic (citraconic) acid with diimide in deuterium oxide gave samples of racemic *threo*-[2,3-$^2H_2$]- and *erythro*-[2,3-$^2H_2$]-methylsuccinic acid, respectively, which were converted into the dimethyl esters. In the corresponding region of the 220-MHz NMR spectrum the *threo*-dimethyl ester gave only one signal, at 2.35 ppm, and the *erythro*-dimethyl ester gave a signal at 2.70 ppm.

This assignment of the NMR signals was the basis for interpretation of the following enzymatic experiments:

Deuterated ethylmalonyl-CoA *(1a)* was prepared in deuterium oxide and then treated in the same solvent with a methylmalonyl-CoA-mutase preparation (from *Propionibacterium shermanii*) containing epimerase; this procedure ensured the presence of deuterium at C-2. On hydrolysis of the products methylsuccinic and ethylmalonic acid were obtained in the ratio 11 : 4, which proves that the epimerase is active also with ethylmalonyl-CoA.

The dimethyl ester of the (*R*)-methylsuccinic acid *(2a)* (ORD) obtained in this way contained 95% of monodeuterated molecules (MS). The signal at 2.70 ppm was absent from the 220-MHz NMR spectrum, so that the sample must have been (2*R*,3*S*)-[3-^{2}H]-methylsuccinic acid.



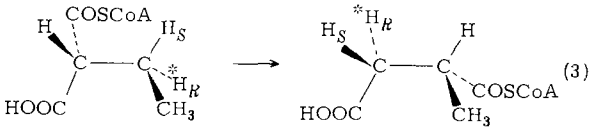
(1) *(2)*

(a), R = D, R' = H; *(b)*, R = H, R' = D

From this result it follows that the replacement at C-2 of the ethylmalonyl-CoA occurs with retention.

To round off the stereochemical picture we still needed a sample of ethylmalonyl-CoA stereospecifically deuterated in the methylene group. Starting from (*R*)-[1-^{2}H]-ethanol[9], prepared enzymatically[10], we synthesized (3*S*)-[3-^{2}H]-ethylmalonic acid by alkylating diethyl malonate with the derived ethyl *p*-toluenesulfonate. The configurational inversion expected to occur during the replacement was confirmed by decarboxylating the deuterated ethylmalonic acid to (3*S*)-[3-^{2}H]-butyric acid and measuring its ORD curve[11].

Mono-coenzyme A derivative *(1b)* of the (3*S*)-[3-^{2}H]-ethylmalonic acid thus prepared and characterized was converted by methylmalonyl-CoA-mutase into (2*R*)-2-methylsuccinyl-CoA, which, on hydrolysis and treatment of the acid component with diazomethane, gave the dimethyl ester *(2b)* and this was studied by mass and NMR spectroscopy. The mass spectrum confirmed complete retention of the hydrogen isotope during the enzymatic reaction. The location of this isotope in the methine position followed from the NMR spectrum.



(3)

Thence it follows that reaction with the methylmalonyl-CoA-mutase from *Propionibacterium shermanii* involves the 3-H_R atom of the ethylmalonyl-CoA and that the replacement at C-3 also occurs with retention (eq. 3).

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German version: Angew. Chem. *85*, 721 (1973)

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The First Oxoferrate(III) Having a Discrete Anion: $K_6[Fe_2O_6]$[1]

By *Hilmar Rieck* and *Rudolf Hoppe*[*]

During our studies on the hitherto rather neglected K/Fe/O system we have found that heating of intimate mixtures of binary oxides ($KO_{0.56}$+"$FeO_{1.0}$" with K:Fe=2.2:1; Fe bomb tube, 600 °C, 7 d) leads to red monoclinic single crystals having lattice constants $a=7.13_4$, $b=11.12_3$, $c=6.51_5$ Å; $\beta=102.3°$, shown to have the composition K_3FeO_3 ($R=R'=5.5\%$) by three dimensional structural analysis employing direct methods (706 *hk*0–*hk*9, diffractometer data, Mo-Kα). The space group is C2/m-C_{2h}^3; Table 1 lists the atomic parameters.

Table 1. Atomic parameters for $K_6[Fe_2O_6]$ (standard deviations in units of last decimal place given in parentheses).

	position	*x*	*y*	*z*	B[Å^2]
K^1	4g	0.	0.2621(1)	0.	1.67(2)
K^2	4h	0.	0.1894(1)	0.5	1.41(2)
K^3	4i	0.3735(1)	0.	0.6468(2)	1.69(3)
Fe	4i	0.1682(1)	0.	0.1440(1)	0.77(1)
O^1	4i	0.9001(4)	0.	0.1628(5)	1.53(9)
O^2	8j	0.2921(3)	0.1366(2)	0.2650(3)	1.45(6)

Table 2. Interatomic distances in $K_6[Fe_2O_6]$ up to 5 Å.

	K^1	K^2	K^3	Fe	O^1	O^2
K^1	3.57_7(2×)	3.35_7(2×)	3.49_6(2×)	3.21_4(2×)	3.23_3(2×)	2.74_4(2×)
		4.32_0(2×)	4.85_0(2×)	3.80_1(2×)	3.87_0(2×)	2.77_8(2×)
						4.83_5(2×)
						4.86_3(2×)
K^2	3.35_7(2×)	3.81_6(2×)	3.37_1(2×)	3.52_5(2×)	3.01_4(2×)	2.70_8(2×)
	4.32_0(2×)	4.20_4	3.74_9(2×)	4.53_9(2×)	4.98_8(2×)	2.89_8(2×)
				4.61_6(2×)		4.60_4(2×)
						4.98_8(2×)
K^3	3.49_6(2×)	3.37_1(2×)	2.89_4	3.26_0	2.52_8	2.78_1(2×)
	4.85_0(2×)	3.74_9(2×)		3.29_2	4.10_3	2.87_0(2×)
				3.83_1	4.46_9	4.28_4(2×)
				4.36_5		4.45_5(2×)
Fe	3.21_4(2×)	3.52_5(2×)	3.26_0	2.71_0	1.94_2	1.84_9(2×)
	3.80_1(2×)	4.53_9(2×)	3.29_2		1.95_3	4.05_5(2×)
		4.61_6(2×)	3.83_1		4.64_5	4.87_9(2×)
			4.36_5			
O^1	3.23_3(2×)	3.01_4(2×)	2.52_8	1.94_2		3.12_9(2×)
	3.87_0(2×)	4.98_9(2×)	4.10_3	1.95_3		3.21_2(2×)
			4.46_9	4.64_5		4.19_2(2×)
						4.50_5(2×)
						4.77_3(2×)
O^2	2.74_4	2.89_8	2.78_1	1.84_9	3.12_9	3.04_3
	2.77_8	2.70_8	2.87_0	4.05_5	3.21_2	3.78_2
	4.83_5	4.60_4	4.28_4	4.87_9	4.19_2	4.11_0
	4.86_3	4.98_8	4.45_5		4.50_5	4.20_9
					4.77_3	4.36_6(2×)
						4.80_9
						4.85_4

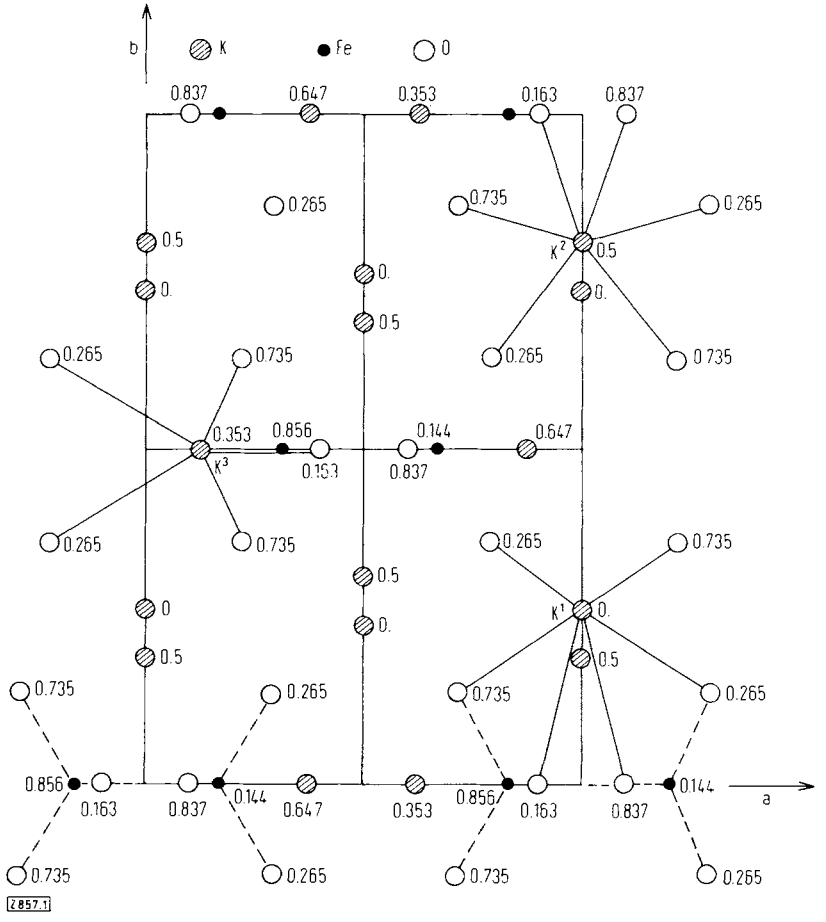

Fig. 1. Crystal structure of $K_6[Fe_2O_6]$; [001] projection. Height in fractions of *c*.

Surprisingly, the compound proves to be the first oxoferrate(III) with a discrete anion whose structure (two tetrahedra sharing a common edge, cf. Fig. 1 and Table 2) resembles that of the Fe_2Cl_6 molecule.

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Since the anion of $K_4[Ag_4O_4]$[2] is planar like the Ag_4Cl_4 molecule, that of $K_2[NiO_2]$[3] linear like the $NiCl_2$ molecule, and that of $Li_4[CoO_4]$[4] tetrahedral like the hypothetical $CoCl_4$ molecule, the structures of the discrete anions in other, as yet unknown transition metal oxides having high cation populations may reasonably be expected to resemble those of the corresponding chlorides.

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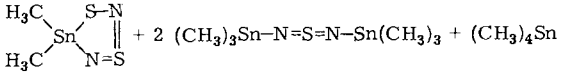
$(CH_3)_2SnS_2N_2$: A Compound Containing a Five-membered Tin-Sulfur-Nitrogen Ring[**]

By *Herbert Roesky* and *Hartmut Wiezer*[*]

Tetrasulfur tetranitride *(1)*[1] reacts almost quantitatively with tris(trimethylstannyl)amine *(2)* in the molar ratio 1:2, affording 5,5-dimethyl-1,3λ⁴,2,4,5-dithiadiazastannole *(3)*, sulfur *N,N'*-bis(trimethylstannyl)diimide *(4)*[2] and tetramethylstannane *(5)*.

$$S_4N_4 + 2\ [(CH_3)_3Sn]_3N \longrightarrow$$
(1) *(2)*



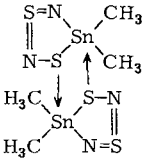
$+ 2\ (CH_3)_3Sn{-}N{=}S{=}N{-}Sn(CH_3)_3 + (CH_3)_4Sn$

(3) *(4)* *(5)*

However, according to IR investigations the first products from *(1)* and *(2)* are only *(4)* and sulfur. *(3)* and *(5)* are formed on vacuum-sublimation of the primary products at 45 °C/*ca.* 0.01 torr. Nucleophilic attack of the sulfur on one Sn atom of *(4)* then leads to ring closure with migration of a methyl group.

(3) is a yellow compound, solid at room temperature, decomposes at 198 °C, but can be recrystallized from CH_2Cl_2. It was characterized by elemental analysis and by its mass spectrum: $m/e = 242$ molecular ion (rel. intensity 58%), 227 $M-CH_3$ (100), 212 $M-2CH_3$ (5), 196 $(CH_3)_2SnSN$ (4), 181 CH_3SnSN (16), 166 SnSN (12), 135 CH_3Sn (33), 120 Sn (23), 46 SN (42); the tin-containing fragments are cited only for ^{120}Sn.

Cryoscopic determination of molecular weight in benzene (found 489) and osmometric determination in chloroform (found 479) afford, contrary to determination in the gas phase, double the relative molecular mass for *(3)* in solution, which we conclude indicates a dimeric structure.



According to the ^1H-NMR spectrum at room temperature (TMS externally) the methyl groups are equivalent: $\delta = -0.95$ ppm; $J_{H-^{117}Sn} = 66.3$, $J_{H-^{119}Sn} = 69.3$ Hz. The IR spectrum (KBr disc) shows absorptions at 2960 w, 2880 w, 1393 w, 1186 w, 1064 s, 1034 vs, 901 s, 778 s, 737 w, 701 s cm^{-1}.

Experimental:

$[(CH_3)_3Sn]_3N$ (11.5 g, 2.28 mmol), dissolved in CH_2Cl_2 (50 ml), is dropped with stirring into a suspension of S_4N_4 (2.1 g, 1.14 mmol) in CH_2Cl_2 (150 ml) at −20 °C. After warming slowly to room temperature (1 h), the solvent is removed in a vacuum. When the yellowish-red solid residue is heated, *(5)* (1.8 g, 86%) passes at 45 °C/*ca.* 0.01 torr into a condensation trap, and *(4)* separates on a sublimation finger; *(3)* (2.5 g, 91%) can be isolated from the residue by recrystallization from CH_2Cl_2.

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[**] This work was supported by the Fonds der Chemischen Industrie.

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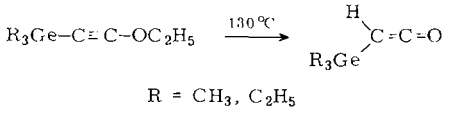
Silyl-, Germyl-, and Stannyl-substituted Ketenes

By *S. V. Ponomarev*[*]

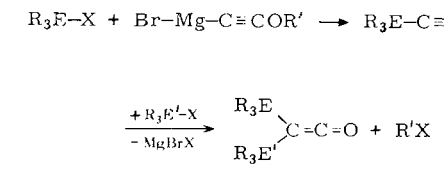
1965 saw the synthesis of (trimethylsilyl)ketene as the first ketene derivative in which a H atom was replaced by a homolog of carbon[1]. When studying the pyrolysis of germyl and stannyl derivatives of alkoxyacetylenes we found that the germyl and stannyl derivatives behaved differently: for instance, ethoxy(germyl)acetylenes gave monosubstituted germylketenes:



$R = CH_3, C_2H_5$

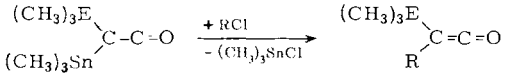
but bis(trimethylstannyl)ketene was formed on pyrolysis of ethoxy(trimethylstannyl)acetylene.

We have developed an adaptable method for preparation of such bis(organometallic) derivatives of ketene, in which an (alkoxyethynyl)magnesium bromide is treated with an excess of trialkylzinc or trialkylgermanium halide[2]:



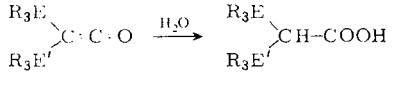
E = E' = Ge, Sn;
E = Si, E' = Ge, Sn; R = Me, Et, Pr; R' = Et, Bu

The stannylgermyl- or stannylsilyl-ketenes react readily with germyl or boryl halides, the stannyl groups being replaced by germyl or boryl groups[3]:



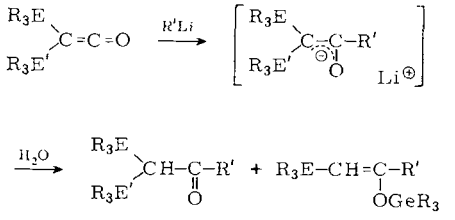
E = Si, Ge; R = Cl_3Ge, $(C_4H_9)_2B$

The bis(organometallic)ketenes are converted into the corresponding acetic acids by aqueous dioxane[4]:

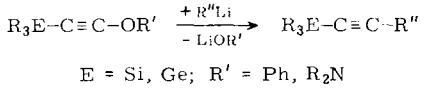


E = E' and E ≠ E' = Si, Ge

Treatment with organolithium compounds and subsequent hydrolysis afford the corresponding ketones and germyl-substituted enols[5]:

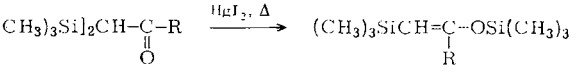


The metalated acetylene derivatives also react with alkyllithiums, but then the alkoxy group is removed by the nucleophile[6]:

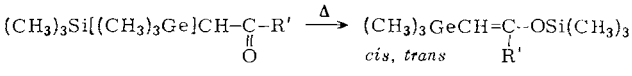


E = Si, Ge; R' = Ph, R_2N

Bissilylated ketones rearrange when heated or in the presence of HgI_2:



Only the trialkylsilyl group migrates in ketones containing different substituents:



This group can be removed as butyltrimethylsilane by butyllithium.

Lecture at Giessen (Germany) on May 4, 1973 [VB 370 IE]
German version: Angew. Chem. 85, 673 (1973)

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[1] *L. L. Schukovskaya, R. I. Pal'chik,* and *A. N. Lasarev,* Dokl. Akad. Nauk SSSR *164,* 357 (1965).

[2] *S. V. Ponomarev, M. B. Erman, S. A. Lebedev, C. Ja. Petschurina,* and *I. F. Lutsenko,* Zh. Obshch. Khim. *41,* 127 (1971).

[3] *S. V. Ponomarev, M. B. Erman,* and *L. L. Gerwitz,* Zh. Obshch. Khim. *42,* 469 (1972).

[4] *S. A. Lebedev, L. L. Gerwitz, S. V. Ponomarev,* and *I. F. Lutsenko,* Zh. Obshch. Khim., in press.

[5] *S. A. Lebedev, S. V. Ponomarev,* and *I. F. Lutsenko,* Zh. Obshch. Khim. *42,* 647 (1972).

[6] *S. A. Lebedev, O. A. Zacharova, S. V. Ponomarev,* and *I. F. Lutsenko,* Zh. Obshch. Khim., in press.

[7] *S. V. Ponomarev* and *S. A. Lebedev,* unpublished work.

Reviews

Abstracts of selected progress reports and review articles

The reactions of hydrogen atoms in aqueous solutions are the subject matter of a review by *P. Neta*. The H atoms are generated, for instance, by radiolysis of water, reaction of hydrated electrons with acids, or photolysis of an organic compound (such as RSH) in solution. The reactions of the H atoms were studied by the observation of short-lived intermediates (*e.g.* by pulse radiolysis or ESR spectroscopy). The reactions of H atoms in aqueous solutions appear to be more selective than those of organic radicals. [Reactions of Hydrogen Atoms in Aqueous Solutions. Chem. Rev. *72*, 533—543 (1972); 65 references]

[Rd 610 IE—M]

The reduction of unsaturated organic compounds by the systems sodium/alcohol/ammonia (Birch reduction, A) and Li/lower amines (Benkeser reduction, B) is the subject of a comparative study by *E. M. Kaiser*. The article deals with the reduction of aromatic hydrocarbons, alkynes, alkenes, unsaturated ethers, acetals and ketals, unsaturated alcohols and amines, aromatic nitro compounds, carboxylic acids, ketones, epoxides, 5- and 6-membered heterocycles, and a number of S compounds. Saturated or partially saturated derivatives are generally obtained. The reaction is accompanied by reductive cleavage. B is usually more effective but less selective than A. However, the selectivity of B can be enhanced by suitable solvents. Reductive amination is also possible. [A Comparison of Methods Using Lithium/Amine and Birch Reduction Systems. Synthesis *1972*, 391—415; 133 references]

[Rd 614 IE—M]

Determination of the effective charges of anions by the positron method is reported by *G. M. Bartenev, A. Z. Varisov, V. I. Gol'danskii, E. P. Prokop'ev*, and *A. D. Tsyganov*. The annihilation of positrons by the electrons of a substance is usually accompanied by the emission of two γ quanta. This phenomenon offers two possibilities of determining the effective charges of anions: by measuring the angular distribution of the annihilation radiation or by measuring the lifetime of the positrons. Experimental data are given for about 100 oxides and salts. [Determination of the Effective Charges of Anions in Media of the Ionic Type by the Positron Method. Russ. Chem. Rev. *41*, 305—313 (1972); 67 references]

[Rd 622 IE—Q]

The insertion of isocyanides into metal-carbon bonds and reactions of coordinated isocyanides are reviewed by *Y. Yamamoto* and *H. Yamazaki*. Reactions of isocyanides with complexes having a metal-carbon σ-bond, with "carbene" complexes, and with metal azides are discussed, as well as reactions of isocyanide complexes with alkyllithium and Grignard reagents, with amines and alcohols, and oxidative additions of alkyl halides to isocyanide complexes. These reactions receive considerable attention because in some respects they resemble organic syntheses, especially polymerization reactions, catalyzed by transition metal ions. [Isocyanide Insertion and Related Reactions. Coord. Chem. Rev. *8*, 226—239 (1972); 47 references]

[Rd 629 IE—H]

Recent concepts relating to inorganic peroxo compounds are summarized by *I. I. Vol'nov*. A survey of existing data for the anions O_2^{2-}, O_2^-, and O_3^- is followed by descriptions of the structures of the simple and complicated peroxo compounds. In conclusion a scheme is presented for their classification. [Modern Views of the Nature of Inorganic Peroxy-Compounds. Russ. Chem. Rev. *41*, 314—322 (1972); 93 references]

[Rd 623 IE—Q]

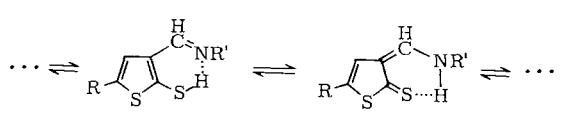
Advances in isocyanate chemistry from 1960 to 1971 are reported by *S. Ozaki*. The most significant of the numerous (more than 25) methods for the synthesis of isocyanates is the phosgenation of amines or their salts. The reaction of nitro compounds with carbon monoxide in the presence of noble metal compounds represents a new, one-step process. Apart from the frequently exploited nucleophilic additions of isocyanates, additions to double bonds, polymerizations, cyclizations, and insertions of the isocyanate group into Si—N, N—B, C—O, and other bonds have also been the subject of recent detailed studies. [Recent Advances in Isocyanate Chemistry. Chem. Rev. *72*, 457—496 (1972); 496 references]

[Rd 616 IE—M]

Coupling reagents for peptide synthesis are dealt with by *Y. S. Klausner* and *M. Bodansky*. Unsaturated ethers such as α-chlorovinyl ethyl ether convert N-protected amino acids initially into the chloride.—Addition of nucleophilic hydroxy compounds, *e.g.* pentachloro- and pentafluorophenol, reduces the racemization occurring during the activation of acyl peptides with dicyclohexylcarbodiimide. Of particular utility are the enol esters accessible from 1,2-oxazolium salts and carboxylic acids, which react with amino acid esters. Other coupling reagents include cyanamides, keteneimines, ketenes, ynamines, and acyloxyphosphonium ions. [Coupling Reagents in Peptide Synthesis. Synthesis *1972*, 453—463; 86 references]

[Rd 618 IE—M]

Syntheses and properties of new complex-forming thiophene derivatives—mercapto-, dimercapto-, and 3-alkyliminomethyl-2-mercaptothiophenes—are described by *Ya. L. Gol'dfarb* and *M. A. Kalik*. According to the NMR spectra, compounds *(1)* exist mainly in the form *(1a)*. The authors



(1) *(1a)*

also go into chelate formation by these thiophene derivatives and reactions of the metal chelates. [The Synthesis and Properties of New Complex-Forming Thiophen Derivatives. Russ. Chem. Rev. *41*, 360—370 (1972); 100 references]

[Rd 628 IE—Q]

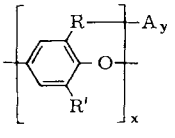
The chemistry of tetravalent niobium and tantalum and of trivalent zirconium and hafnium is reviewed by *D. A. Miller* and *R. D. Bereman*. All pertinent compounds have in common an extreme sensitivity toward oxygen and moisture; many conflicting data about these substances can therefore be found in the literature. These data are quoted non-critically. [The Chemistry of d^1 Complexes of Niobium, Tantalum, Zirconium, and Hafnium. Coord. Chem. Rev. 9, 107—143 (1972); 95 references]

[Rd 635 IE—H]

Patents

Abstracts of selected "Deutsche Offenlegungsschriften" (DOS), *i. e.* provisionally published specifications as filed with the German Patent Office

A membrane of phenolic polyether *(1)*, which is itself known, is prepared by dissolution of the polymer in a mixture consisting of two solvents for the polymer with different



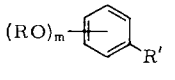
(1)

R = phenyl; R′ = phenyl, alkylphenyl, biphenylyl, terpenylyl, naphthyl; A = halogen; y = 0, 1, 2, 3, or 4; x is such that the specific viscosity of the polymer is between 0.3 and 1.5 (in cyclohexanone at 25 °C)

boiling points, casting on a support, and removal of at least part of the solvent having the lower boiling point. The resulting film is treated with a coagulant liquid and finally dried. It has a non-porous layer 0.1 to 10 μm thick and a porous layer 30 μm to 1 mm thick with open pores, the total volume of the pores constituting 20—80% of the total volume of the membrane. It can be advantageously used for the fractionation of gas mixtures containing oxygen, nitrogen, hydrogen, carbon dioxide, helium, or methane or for the separation of liquid mixtures by pervaporation. [DOS 2153646; Rhône-Poulenc S.A., Paris]

[PR 64 IE—Ö]

A new isomerization catalyst with which unconjugated alkenylalkoxybenzenes *(1)* can be almost quantitatively converted into the conjugated compounds is obtained by heating a mixture of alkali metal, alkali metal hydroxide, and aluminum oxide, possibly under an inert gas, to temperatures above the melting point of the alkali metal (200—500 °C). The alkali metal may be used as an alloy,



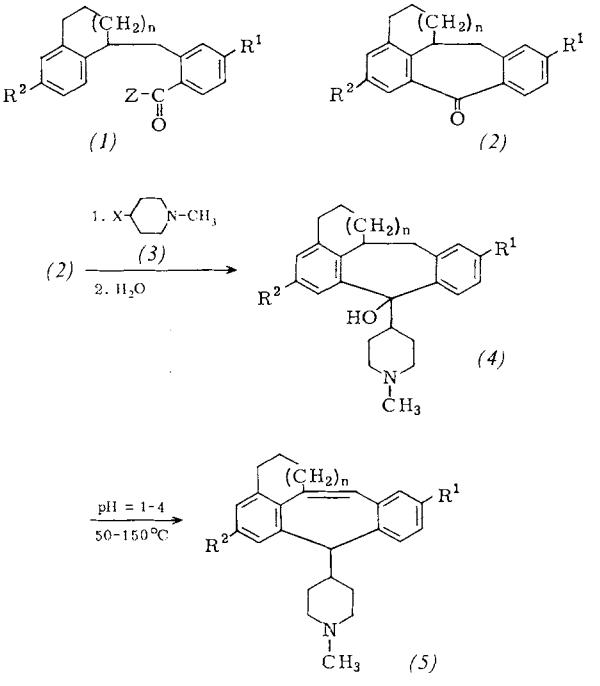
(1)

m = 1—5; R = alkyl (C_1—C_6), aralkyl, or, if $m \geq 2$ and at least 2 R are adjacent, together with the other residue a lower alkylene bridge; R′ = alkenyl residue, whose double bond is not conjugated with the benzene ring.

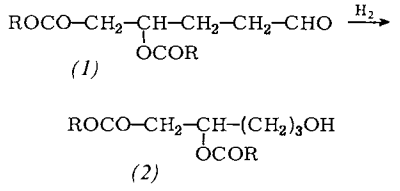
e.g. Na-K-alloy. One can also use several hydroxides, which need not correspond to the alkali metals used. The aluminum oxide support may be in any modification or may be in the form of a compound containing Al_2O_3, *e.g.* kaolin. One part by weight of alkali metal hydroxide is preferably used per 100—1 parts by weight of Al_2O_3, and 1 mol of alkali metal per 1—100 mol of alkali metal hydroxide. The catalyst can also be prepared by heating an alkali metal with aluminum oxide containing physically mixed water, water of crystallization, or OH groups that can be eliminated as water. The water content is usually 1.3—15 wt.%. The alkali metal is preferably used in a 1.01- to 2-fold amount. The catalyst, unlike dispersion catalysts, contains no free alkali metal. It is stable to air and water and remains catalytically active for a long time. Unlike with the acidic or basic isomerization catalysts used in the past, the compounds *(1)* can be rearranged even at room temperature with the new catalyst. The process may be carried out continuously or discontinuously, preferably under an inert gas. One part by weight of catalyst is used per 1000—1 parts by weight of *(1)*. For example, safrole can be quantitatively isomerized to isosafrole, or *o*-allylanisole to *o*-anethole. [DOS 2157534; Sumitomo Chemical Co. Ltd., Osaka]

[PR 79 IE—V]

Piperidylpleiadenes *(5)* **and piperidylpleiadenols** *(4)* are spasmolytic and can act as anticonvulsants. They are prepared by ring closure of the acids or acid derivatives *(1)* to form the ketones *(2)* (mineral acid or Friedel-Crafts



(1) *(2)* *(4)*



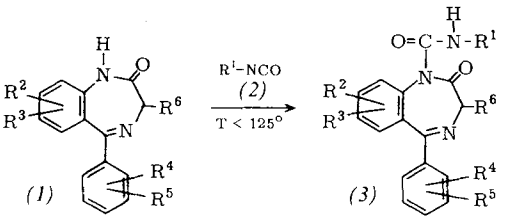
(1) is obtainable by the oxo synthesis from 1-vinylethylene diacylates. 1,2,5-Pentanetriol can be obtained from *(2)* by transesterification with methanol in the presence of an acidic catalyst. The OH group of *(2)* can be selectively etherified, esterified, ethoxylated, halogenated, and sulfonated. [DOS 2105968; Badische Anilin- & Soda-Fabrik AG, Ludwigshafen]

[PR 102 IE—B]

High-impact thermoplastic graft copolymers of the ABS and MBS type (ABS = acrylonitrile/butadiene/styrene, MBS = methyl methacrylate/butadiene/styrene) can be prepared as follows by bulk or bulk-suspension polymerization. Preformed rubbery polymer A and preformed polymer B are dissolved in a mixture of graft monomers, and this mixture is polymerized with agitation to a conversion of 10 to 40% to form a dispersion in which the polymers A and B are dispersed in a solution of the polymer of the graft monomers in the remaining graft monomers; the latter are polymerized further in bulk or in aqueous suspension to a conversion of at least 50%. The polymer A is a polydiolefin with a high 1,4 content, and the polymer B is a 1,3-butadiene polymer. The latter is selected from homopolymers of 1,3-butadiene with at least 50% 1,2-linkage and copolymers of 1,3-butadiene with less than 50 wt.% of a copolymerizable monomer. The graft monomers comprise mixtures of styrene or a styrene homolog with acrylonitrile, its homologs, methyl methacrylate, or its homologs. The economical bulk and bulk-suspension process has until now been confined to the high-impact polystyrene resins, whereas ABS and MBS resins having good properties were obtainable only by the more expensive emulsion graft copolymerization. [DOS 2063291; Polymer Corp., Sarnia, Ontario]

[PR 69 IE—S]

Benzodiazepinecarboxamides *(3)* and their pharmacologically acceptable acid addition salts can be used as tranquillizers and sedatives for mammals and birds. They can be prepared by reaction of the benzodiazepines *(1)* with excess isocyanate *(2)* in inert organic solvents, preferably ethers. Some acid addition salts can also be used as mothproofing agents (*e.g.* the hexafluorosilicates) or herbicides (*e.g.* the trichloroacetates). [DOS 2149326; The Upjohn Co., Kalamazoo, Mich.]



R^1 = alkenyl (C_3—C_8), cycloalkyl (C_3—C_6), halogenoalkyl (C_2—C_6); R^2, R^3, R^4, R^5 = H, F, Cl, Br, CN, CF_3, alkyl (C_1—C_3); R^6 = H, alkyl (C_1—C_3)

[PR 92 IE—N]

New compounds of the type *(1)* **with hydrogen bonds** are obtained by reaction of at least 1% of a polyhydroxy compound having two or more OH groups, such as propylene glycol, glycerol, or polyoxyethylene glycol (MW 200—1000), with an iodophore (iodine adduct), such as polyvinylpyrrolidone-iodine or nonylphenoxypoly(ethylenoxy)ethanol-iodine complex. *(1)* is used in skin cleaners with

[R] · X *(1)* R = iodophore, X = polyhydroxy compound

a scouring action, which, in addition to the compound *(1)*, which has an antiseptic action, also contain a detergent, such as alkylsulfonic esters, Na *N*-cyclohexyl-*N*-palmitoyltaurate, Na *N*-fatty acid-*N*-methyltaurate, Na *N*-methyl-*N*-palmitoyltaurate, or Na lauryl sulfate, a substance with an abrasive action such as pumice, kaolin, or sand with a particle size of 100—1000 µm, and a pharmaceutically acceptable vehicle, *e.g.* polyoxyethylene glycol (MW 1500—6000). The cleaners can be used for the treatment of acne wounds contaminated with pathogens. [DOS 2105057; Mundipharma AG, Rheinfelden]

[PR 107 IE—Z]

To cleave thioacetals to form the carbonyl compound, the thioacetals are allowed to react with an alkylating agent such as methyl iodide in the presence of water and possibly a basic agent such as alkali metal carbonate or alkaline earth metal carbonate. Examples are the cleavage of 3-hydroxy-6,6-ethylenedithioandrostane, 3-hydroxy-20,20-ethylenedithio-5-pregnene, and 24,24-ethylenedithiocholane. [DOS 2204116; Roussel-Uclaf, Paris]

[PR 111 IE—B]

Determination of Organic Structures by Physical Methods. Vol. 3. Edited by *F. C. Nachod* and *J. J. Zuckerman*. Academic Press, New York—London 1971, 1st Edit., 472 pp., numerous figures and tables, bond $ 22.50.

Volume 3 contains articles on photoelectron spectroscopy, X-ray diffraction, optical rotatory dispersion and circular dichroism, thermochemistry, mass spectrometry, and electron spin resonance, as well as a section on "Configuration and Conformation by NMR".

C. R. Brundle and *M. B. Robin* describe the two classes of photoelectron spectroscopy, *i.e.* Turner molecular photoelectron spectroscopy (photoemission by short-wave UV radiation below 60 eV) and Siegbahn "Electron spectroscopy for chemical analysis" (abbreviated to ESCA photoemission by X-rays above 1000 eV). The effects of the molecular environment on the ionization potentials of the electrons of an atom in the molecule (chemical shifts) are described. Line splitting due to unpaired electrons, Jahn-Teller symmetry distortions, and spin-orbit coupling are discussed. A survey of the relations between certain structural characteristics and the chemical shifts of the ionization potentials underlines the importance of these data as structural parameters.

R. F. Stewart and *S. R. Hall* explain fundamental concepts and methods of X-ray diffraction. Their application to the identification of atoms and to the determination of bond lengths, bond angles, configurations, and steric structures of molecules is outlined. Possibilities of structural analysis as a result of the defects produced by incident X-rays and the determination of charge-density profiles of organic molecules with the aid of X-ray diffraction are illustrated by a number of examples.

P. Crabbe presents an introduction to ORD and CD spectroscopy, and outlines the effects of solvent, temperature, configuration, and conformation on the Cotton effects. The CD and ORD characteristics of numerous chromophores are described. The author explains Cotton effects of polypeptides and synthetic, optically active high polymers, as well as the application of CD and ORD spectroscopy to the determination of the α-helix content of such macromolecules. The knowledgeable reader will perhaps note the absence of any reference to magnetic circular dichroism and MORD spectroscopy.

The section "Thermochemistry", by *K. B. Wiberg*, deals with the measurement and evaluation of enthalpies of combustion, hydrogenation, isomerization, hydrolysis, ionization, and protonation, as well as the determination or estimation of rotation barriers and bond energies from thermodynamic and spectroscopic data. Classical and quantum-mechanical approximation methods for the calculation of thermodynamic molecular data are outlined.

D. Williams, in his article on "Mass Spectrometry", concentrates on energy and kinetic aspects of fragmentation reactions and on the structure of fragment ions. The use of mass spectrometry for the elucidation of structures of natural products is illustrated by examples such as the sequencing of peptides and the fragmentation of trimethylsilyl nucleosides and nucleotides in the field ion mass spectrometer.

G. A. Russel devotes his article on electron spin resonance to the incorporation of spin labels in organic molecules and the associated side reactions. Hyperfine splitting due to coupling with neighboring and remote unpaired electrons and magnetic nuclei (^{1}H, ^{13}C, ^{19}F) is discussed.

A criterion for distinguishing between the closely related concepts of configuration and conformation is the much shorter time scale of conformational changes. In this sense, *F. A. L. Anet* and *R. Anet* deal in the final section "Configuration and Conformation by NMR" with the use of NMR data such as coalescence temperatures, chemical shifts, coupling constants, and nuclear Overhauser effects for the determination of configurations and conformations.

All the articles are clearly written, and in accordance with the conception of the work, they concentrate on the application of the physical methods. Even those who are not very familiar with these fields are therefore provided with a survey of physical structural analysis. The lists of references, which consist almost exclusively of original sources in English published up to 1970, are fairly comprehensive, and together with numerous tables, they qualify Volume 3 for use as a reference work.

Eberhard Breitmaier [NB 121 a IE]

Determination of Organic Structures by Physical Methods. Vol. 4. Edited by *F. C. Nachod* and *J. J. Zuckerman*. Academic Press, New York—London 1971, 1st Edit., 381 pp., numerous figures and tables, bound $ 19.50.

Volume 4 is devoted to subsidiary fields of NMR spectroscopy that have gained importance through very recent developments and refinements of the NMR technique. The methods described have become more accessible to organic and inorganic structural chemists through the availability of mass-produced multichannel NMR spectrometers having high magnetic fields with facilities for frequency sweep and pulse operation as well as suitable computers.

W. Naegele, in Section 1, presents a brief introduction to the theory and instrumentation of high-field NMR spectroscopy. He then concentrates on applications to the determinations of structures of organic molecules. Considerable space is given to the 220 MHz ^{1}H-NMR spectroscopy of natural and synthetic polymers.

Section 2, by *N. Boden*, deals with pulse NMR spectroscopy and its use in the measurement of Fourier transform NMR spectra, in the measurement of spin-lattice relaxation times, and above all in spin echo experiments.

The methods of homonuclear and heteronuclear magnetic double resonance, which are necessarily also touched upon in other chapters of the volume, are the subject of Section 3 by *W. McFarlane*.

R. L. Lichter, *P. R. Wells*, *P. S. Pregosin*, *E. W. Randall*, and *J. R. van Wazer* describe, in Sections 4 to 7, methods and applications of hetero-NMR spectroscopy, mainly with the nuclei ^{15}N, ^{13}C, ^{31}P and with ^{7}Li, ^{29}Si, ^{77}Se, ^{117}Sn, ^{119}Sn, ^{195}Pt, ^{199}Hg, ^{205}Tl, and ^{207}Pb as the measuring probes.

The authors have managed to provide the reader with a great deal of information through illustrations, tables, and presentation. Large lists of references (which, however,

cite almost exclusively original sources in English) provide an opportunity for further reading on the topics discussed.

The description of recent developments and refinements and the treatment of numerous nuclei that were formerly not very common will provide stimulating material in particular for structural analysts and NMR spectroscopists. The presence of a number of gaps in the sections is unavoidable in view of the flood of literature and the rapid development of NMR spectroscopy.

Eberhard Breitmaier [NB 121 b IE]

New Techniques in Amino Acid, Peptide and Protein Analysis. Edited by *A. Niederwieser* and *G. Pataki*. Ann Arbor–Humphrey Science Publ., Inc., Ann Arbor Mich. 1971. 1st ed., 461 pp., numerous figures and tables. bound $ 22.50.

The rapid development of a field of science is almost inevitably linked with the development and introduction of new procedures. Thus the biological sciences brought with them considerable advances in chemical methods. The present book, or more precisely its first eight chapters, summarizes new experimental methods in the field of amino acids, peptides, and proteins: 1. ion-exchange chromatography of amino acids and peptides; 2. and 3. gas chromatography of amino acids and peptides (these two chapters overlap to some extent); 4. mass spectrometry of peptides; 5. molecular sieve chromatography; 6. thin layer gel filtration; 7. microelectrophoresis and synthesis of proteins in quantities of 10^{-7} to 10^{-9} g; 8. protein electrofocusing. The last two chapters (chemical accessibility and environment of amino acid residues in natural proteins and methods for the study of the quaternary structure of proteins), on the other hand, are surveys of methods with fairly superficial descriptions of techniques.

The editor has allowed the authors an individual approach to their own chapters. Overlapping occurs in places. However, the book as a whole will be successful in the editor's aim of presenting reliable surveys of the new experimental methods.

Karel Bláha [NB 138 IE]

Chemistry of Fungicidal Action, Molecular Biology, Biochemistry, and Biophysics. By *R. J. Lukens*. Springer-Verlag, Berlin–Heidelberg–New York 1972. 1st ed., xiii, 136 pp., 8 figs., bound DM 42.—

The present monograph presents a comprehensive survey of current knowledge on the chemistry of fungicides that are used for the protection of plants or industrial organic materials against destructive fungi. Its purpose is to explain general and common principles of fungitoxic phenomena within the framework of present-day views in cell biology.

The material is divided into the following sections: 1. chemical control of deterioration by fungi (3 pp.), 2. measurement of fungitoxicity (8 pp.), 3. fungitoxic barriers (18 pp.), 4. migration of fungicides to sites of action (8 pp.), 5. sites of action (17 pp.), 6. reaction of fungicides with cell constituents (11 pp.), 7. effects of fungicides on enzymes (9 pp.), 8. structure-activity relationships (15 pp.), 9. action of fungus on fungicide (8 pp.).

The formulas of the fungicides discussed are listed in a seven-page appendix.

The discussion is based on details from 460 references, whose main conclusions are presented succinctly and in a well coordinated manner. The monograph should be a very valuable aid to all biologists, chemists, and toxicologists concerned with phytopathology and microbiology, and should also provide a stimulus to close the gaps, some of them considerable, that still exist in our knowledge of the mode of action of fungicides.

Klaus Sasse [NB 141 IE]

The Raman Effect. Vol. 1. Principles. Edited by *A. Anderson*. Marcel Dekker, Inc., New York 1971. 1st ed., ix, 404 pp., numerous figures, bound $ 28.50.

A fundamental survey of the theoretical and experimental principles of the Raman effect and of its important applications in physics and chemistry is to be presented in two volumes. The book is intended for students and scientists seeking an introduction to the field of Raman spectroscopy. Volume 1 contains the following chapters: 1: Historical Introduction (*R. S. Krishnan*, 48 pp.), a rather long-winded account for the intended readership, with only a few tables, formulas, or critical comments. For example, a half page on "Born's Lattice Dynamics" is followed by a page on "Raman's Lattice Dynamics", with no indication for the beginner of the problem involved in this controversy and with no objective comparison. Chapter 2: Polarizability Theory of the Raman Effect (*G. W. Shantry*, 47 pp.) and Chapter 3: The Theory of the Raman Scattering of Crystals (*R. A. Cowley*, 87 pp.) are worth reading, particularly for physicists. Chapter 4: Raman Instrumentation and Technique (*C. E. Hathaway*, 104 pp.) gives a detailed account of the properties of gas discharge lamps, spectrographs, and photographic plates and of commercial instruments that have long since fallen out of use or been withdrawn from the market, together with detailed information on laser light sources and modern spectrometers. This is followed by Chapter 5: Stimulated Raman Effect (*P. Lallemand*, 56 pp.) and Chapter 6: Brillouin Scattering (*R. S. Krishnan*, 61 pp.), both of which are very good descriptions, which will be of interest in particular to the physicist.

The readers at which the book is aimed would find it more useful if Chapters 1 and 4 were dusted off somewhat and provided with critical comments. The present volume has little to offer the chemist. The applications in the fields of chemistry and physics are to be presented in Volume 2.

Bernhard Schrader [NB 144 IE]

Mechanism in Organic Chemistry. By *R. Alder*, *R. Baker*, and *J. M. Brown*. John Wiley & Sons, Inc., New York—London 1971, 1st Edit., x, 378 pp., numerous figures, bound £ 5.00.

The main purpose of the authors was to summarize in one volume the present situation in mechanistic organic chemistry for advanced students. They assume that the student is familiar with a textbook of organic chemistry (such as that by *Roberts* and *Caserio*) and that he has been introduced to the principles of physical chemistry. The aim of the book is to enable the reader to understand organic reaction mechanisms, to allow critical reading of original articles in this field, and ultimately to enable him to plan and execute his own experiments correctly.

The actual treatment of organic reactions is preceded by a general chapter, in which catalysis, the energies of ground and transition states, and isotope, ring-strain, solvent, steric, electronic, and stereoelectronic effects are discussed.

This is followed by "Dissociative Processes". This section deals with processes that follow the primary cleavage of a carbon bond, *i.e.* reactions of carbenium ions, carbanions, carbenes, and free radicals.

The third chapter surveys "Synchronous Reactions" in substitutions and eliminations.

Electrocyclic and sigmatropic reactions and cycloadditions are discussed in the fourth chapter, "Multicentre Reactions".

The fifth and final chapter is headed "Associative Reactions" and contains reactions in which intermediates having a new carbon bond are formed: electrophilic and free-radical aromatic substitutions, electrophilic and free-radical additions to unsaturated systems, nucleophilic addition-elimination reactions to the carbonyl group, and nucleophilic vinyl and nucleophilic aromatic substitutions.

There is no doubt that the authors have succeeded in making a representative and comprehensible selection from the many articles on organic reaction mechanisms published in recent years, so that the reader in particular who does not work in this field will obtain a general picture. Although it has not been entirely possible to avoid subjective evaluation, this must be attributed to the necessity of limiting the subject matter.

The rapid development of mechanistic organic chemistry and the new results that are continually being found in this field present a problem in the production of an up-to-date book of this nature. As an example, one might mention the S_N2 reaction, which perhaps would not nowadays be assigned without comment to the chapter on "Synchronous Reactions".

If one takes this into account, the book is an excellent supplement to advanced instruction, particularly since each chapter is provided with exercises, and the reader whose interests go beyond the scope of the book is referred to original articles and detailed reviews in 600 references, most of which are recent, and which extend up to 1970.

All in all, "Mechanism in Organic Chemistry" will be equally useful to students and to lecturers.

Gernot Boche [NB 123 IE]

Organophosphorus Chemistry. Vol. 2. Specialist Periodical Reports. Published by The Chemical Society, London 1971. 1st ed., xi, 292 pp., numerous figures, bound £ 7.—.

For the second time a group of Anglo-Saxon specialists under the expert direction of *S. Trippett* has undertaken to present a survey of phosphorus literature published between July 1969 and June 1970 to follow the first volume in this series, which was published in 1970 and covered the literature from the beginning of 1968 until June 1969. As in Volume 1, the arrangement of the material in the second volume is based mainly on the substance, though mechanistic aspects are also considered.

S. Trippett has once again acquired the services of eight expert co-authors, who present a "snapshot" of the present position of phosphorus chemistry based on the evaluation of more than 1200 references.

The material discussed in the second volume is divided into 11 chapters: Phosphines and Phosphonium Salts *(D. J. H. Smith)*; Pentacovalent Phosphorus Compounds *(S. Trippett)*; Halophosphines and Related Compounds *(J. A. Miller)*; Phosphine Oxides *(J. A. Miller)*; Acids of Trivalent Phosphorus and Derivatives *(B. J. Walker)*; Acids of Pentavalent Phosphorus *(N. K. Hamer)*; Phosphates and Phosphonates of Biochemical Importance *(D. W. Hutchinson)*; Ylides and Related Compounds *(S. Trippett)*; Phosphazenes *(R. Keat)*; Photochemistry, Free Radicals, and Deoxygenation Reactions *(R. S. Davidson)*; Physical Methods *(J. C. Tebby)*.

If one overlooks a few inaccuracies and printing errors, the second volume again gives a comprehensive survey of the rich and varied harvest collected in the course of only a year in the phosphorus field.

The importance of this periodical report to the national and international specialist world cannot be valued highly enough, since the standard work on phosphorus chemistry (*Kosolapoff*: Organophosphorus Compounds) is probably now in its last edition and there is already evidence of a literature gap, which can no doubt be closed with the aid of these "Periodical Reports". However, the German specialists, who tend to waste their time in endless meetings in these days of democratization of academic life and therefore frequently neglect the study of the specialist literature, are particularly grateful to their colleagues from a land where democracy has stood the test of time for this effective aid to coping with the literature.

Leopold Horner [NB 128 IE]

Terpenoids and Steroids. Vol. 1. Specialist Periodical Reports. Published by The Chemical Society, London 1971. 1st ed., xi, 557 pp., numerous figures, bound £ 11.—.

The present volume covers the literature between September 1969 and August 1970, but also extends further back for important topics to provide a broader basis for understanding. The material is divided up well: the terpenes into monoterpenes, sesquiterpenes, diterpenes and triterpenes, and carotenoids (with polyterpenes) and biosynthesis of terpenes and steroids, and the steroids into properties and reactions and syntheses.

The material in such a report must of necessity be presented very concisely, in view of its large volume (approx. 2400 references). The readability of the text is nevertheless still good. Formulas and sections of text are clearly arranged. Despite the understandable absence of a subject index, therefore, any desired special topic can be quickly found. The presentation by the various authors appears homogeneous and complete. The two steroid chapters overlap in a few points. The number of errors is within reasonable limits.

The report can be specially recommended to all those working in the terpene or steroid fields. It puts one's own field in its place in the range of topics, provides a check on one's own reading of the original literature, and extends one's vision to neighboring fields that one can no longer follow continuously. However, even chemists who do not specialize in terpenes or steroids will find the book useful, as it presents a collective survey of the publications of one year, and at the same time goes into a certain amount of detail.

It is to be hoped that the further annual issues of the report will be as compact, lucid, and reasonably priced as the first.

Wolfgang Sucrow [NB 139 IE]

Surface Self-Diffusion of Metals. By *G. Neumann* and *G. M. Neumann*. Diffusion Information Center, Solothurn/Switzerland, Bay Village, Ohio/USA 1972. 1st ed., 132 pp., 35 figs., numerous tables, paperback $ 15.—.

The present volume deals with the self-diffusion of metal atoms on the surface of metals under vacuum or in contact with an inert gas (or its own vapor). This limits the subject to some extent, so that important problems in which surface diffusion plays a part such as the electrochemical deposition and dissolution of metals at the metal/electrolyte phase boundary, or the diffusion of foreign substances in heterogeneous catalysis and in gas diffusion electrodes, are not discussed. If this limitation (which was no doubt necessary because of space considerations) is accepted, it must be acknowledged that the subject matter has been presented with commendable lucidity. This applies equally to the arrangement, the clear text, and the graphs and tables, which are also a credit to the printer. However, with the best will, the reviewer was unable to make out the white-black-gray marking mentioned in the text for the first, second, and third layers in the packed-sphere lattice models in Figures 20a—f. The omission of any detailed theoretical discussions, which would have necessitated reference to other literature in any case, makes for smooth reading. The review character of the work makes a subject index unnecessary. The material is clearly divided into four parts: experimental techniques, experimental results, theoretical considerations, and discussion. As a conclusion, one can see the superiority, with regard to information value, of the techniques that enable one to follow the individual motion of distinguishable particles. The present book is successful within the chosen limits.

B. Kastening [NB 150 IE]

Recent Books

The following books have been received by the editor. Detailed reviews will not be published in all cases because of the limited space available under this heading in the journal.

Die Chemische Industrie und ihre Helfer (The Chemical Industry and Ancillaries). Edited by *K. R. Selka*. 1972/73 Edition. Industrieschau Verlagsgesellschaft, Darmstadt. 612 pp., flexible covers. DM 30.—.

Contents: Advertisements and offers; economic situation; technical review and new products; keyword index for sources; index of advertisers.

Block Copolymers. Edited by *D. C. Allport* and *W. H. Janes*. Applied Science Publishers, London 1973. xxiii, 620 pp., bound £ 12.00.

Einführung in die Mathematik für Naturwissenschaftler (Introduction to Mathematics for Scientists). By *G. Kastner*, Bibliographisches Institut, Mannheim 1971. 210 pp., stitched DM 8.90.

Contents: Numbers; vector algebra; determinants and systems of linear equations; limits of series; functions of a real variable; differential calculus; integral calculus; Taylor series; functions of several variables; differential equations.

Einführung in die Massenspektrometrie (Introduction to Mass Spectrometry). By *H. C. Hill*. Translated into German and revised by *H.-F. Grützmacher*. Heyden, Rheine, London, New York 1973. 119 pp., stitched DM 16.—.

Contents: Instruments and sample introduction systems; principles of organic mass spectrometry; fragmentation of positive ions; interpretation of mass spectra.

Liquid Scintillation Counting, Vol. 2. Edited by *M. A. Crook, P. Johnson*, and *B. Scales*. Heyden, London, New York, Rheine 1972. ix, 327 pp., bound DM 72.—

Contents: Proceedings of a Symposium on Liquid Scintillation Counting, organized by the Society for Analytical Chemistry, Brighton, England, September 13—16, 1971.

Ramanspektren (Raman Spectra). By *K. W. F. Kohlrausch*. Reprint of the 1943 1st Edition. Heyden, London, New York, Rheine 1972. xiv, 469 pp., bound DM 135.—

Contents: Introduction; experimental methodology; vibrational modes and vibrational spectra of simple molecules or ions; Raman spectra of organic substances; Raman spectra of inorganic substances; action of intermolecular forces.

Lehrbuch der Textilchemie, einschließlich der textilchemischen Technologie (Textbook of Textile Chemistry, Including Textile-Chemical Technology). By *H. Rath*. 3rd Edit., Springer-Verlag, Berlin, Heidelberg, New York 1972. xii, 881 pp., bound DM 136.—.

Contents: Cellulose fibers; protein fibers, synthetic fibers; inorganic fibers; organic dyes; application of dyes; textile auxiliaries; water in textile factories; materials of construction for textile finishing machinery.

Surface Chemistry and Colloids. Edited by *M. Kerker*. Vol. 7 of the series "Physical Chemistry Series One". Edited by *A. D. Buckingham*. Butterworths, London—University Park Press, Baltimore 1972. 306 pp., bound £ 10.00.—A volume in the series "MTP International Review of Science".

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The Bacterial Flagella and the Flagellar Protein Flagellin[**]

By Wolfram Bode[*]

In comparison with the relatively complicated flagella of all nucleated organisms, most of the actively motile bacteria have very much simpler locomotion organelles. These flagella are long thin filaments with a helical superstructure, anchored at one end in the cell membrane. Helical waves pass along the flagella in the distal direction during locomotion. In the flagella, identical structural units of a single protein species, flagellin, are linked to one another by non-covalent bonds. The flagellin subunits can be separated from one another by mild methods, and their biochemistry as well as their structure and morphology can be investigated in the isolated state. Under certain conditions they can reaggregate *in vitro* to form polymorphous helical filaments, which are practically indistinguishable from intact flagella. In the flagellum, the elongated flagellin molecules have a layered arrangement in about ten parallel strands, which in turn form a hollow cylinder. Since this cylinder is deformed into a large helix, the individual chemically identical flagellin protomers and the protomer strands in the helical flagella are only quasi-equivalent. The conformation and bonding pattern of the individual longitudinal flagellin lines can presumably be controlled *in vivo* by the basal structures, so that movement within the flagellum could conceivably occur as follows. A cyclically induced change in the length of the individual strands could result in an apparent rotation of the helical flagellum. According to hydrodynamic calculations, the resulting forward thrust is sufficient to propel the bacteria at the observed speeds of up to 50 μm/s.

1. Introduction

All flagella of nucleated (eukaryotic) protozoa (*e.g.* Flagellata) and of the motile cellular forms of higher organisms (*e.g.* zoospores, spermatozoa of invertebrates and vertebrates), despite differences in external form and function, exhibit a surprising similarity of fine structure. Two central axial filaments cylindrically surrounded by nine peripheral double fibrils are always embedded in a matrix having little structure and joined to one another by fine secondary fibers[1–3]. It is assumed that the undulating or beating movements of the flagella are produced by contraction or by displacement of these protein fibrils in relation to one another.

The flagella of bacteria are very much smaller and have a simpler structure. In size and structure they resemble the individual peripheral and axial fibrils of the flagella of eukaryotes, and may therefore be regarded as a primitive fundamental type for the more complicated locomotion

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[**] This article is based on a lecture delivered by the author to the Macromolecular Colloquium in Freiburg on March 2, 1972; cf. Angew. Chem. *84*, 357 (1972); Angew. Chem. internat. Edit. *11*, 334 (1972).

organelles. Because of their relatively simple structure, therefore, the flagella of bacteria are presumably the most useful subjects for studies aimed at obtaining fundamental information about the structure and function of contractile biological locomotion elements. In addition to a particularly detailed review[4], the general articles on the bacterial flagella include a number that deal with the locomotion mechanisms of bacteria[3, 5, 6] and with the genetics and structure of the flagella[7–11]. Existing knowledge on the form and fine structure of the flagella will be described below, as well as the presumed manner in which movement occurs within the flagella. The properties of flagellin, particularly its surprising ability to undergo aggregation *in vitro*, will be discussed in special detail.

2. Flagellation and the Form of Flagella

Many bacteria are capable of "swimming" in or on liquid media in the direction of a nutrient gradient. Most bacteria use highly specialized organelles, the flagella, for their active locomotion. Apart from these, there are only a few known motile bacteria without flagella, which move in other ways (*e. g.* spirochetes, myxobacteria[4, 6]).

The arrangement of the flagella on the bacterial cell is species-specific[12]. Bacteria are known with a single polar flagellum, with a flagellum at each cell pole, with a bundle of flagella at one pole or at both poles, or with numerous flagella over the entire cell surface (peritrichous flagellation, see Fig. 1). The flagella are mostly about 10 μm long and

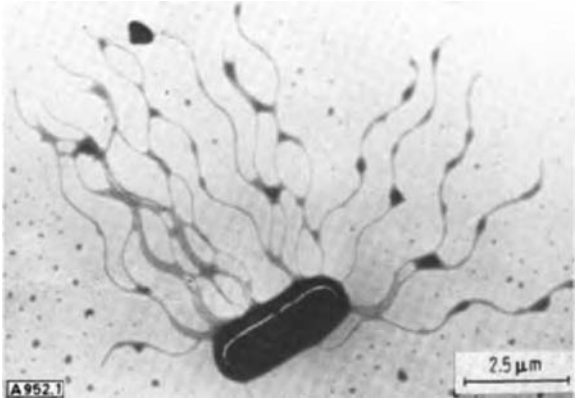

Fig. 1. Electron micrograph of a peritrichally flagellated bacterium (*Proteus mirabilis*) after negative staining with 2% potassium tungstophosphate solution at pH 7.

have a uniform but species-specific diameter of 120 to 200 Å. Both in the attached state and in the free state in solution, they have the shape of a helix[4]. When dried and contrasted on a flat support, the helical flagella collapse and appear under the electron-microscope as sinusoidal filaments, whose species-specific "wavelength" can be roughly equated to the pitch of the original helix and is normally just 2.5 μm for the peritrichous Eubacteriales, such as Proteus bacteria (Fig. 1), Salmonella, and Bacilli (normal type of flagella). Apart from a few paralyzed mutants[9], these normally flagellated bacteria can generally execute relatively rapid rotational and translational movements.

Mutants with low motility and having curly flagella have also been found, the wavelength of these flagella being roughly half of the wavelength of normal flagella, indicating that the pitch of the flagellar helix is roughly halved[4, 9, 10]. Practically immotile mutants with short circular flagella and completely immotile bacteria with perfectly straight flagella can also be observed[4, 10]. These changes in the shape of the flagella are mostly genetic in origin (cf. Section 4). In culture media with very low pH values, however, the short-wave form of flagella has also been observed for wild types of *Proteus mirabilis* that have normal flagella under normal growth conditions[4, 12].

Because they are so thin, single flagella can be observed under the optical microscope only after drying and special mordant staining[6]. In the case of the multiflagellated bacteria, however, the flagella associate during locomotion to form a thick helical bundle. The movement of this bundle of flagella as a whole can be observed under the optical microscope (Fig. 2). During active locomotion the

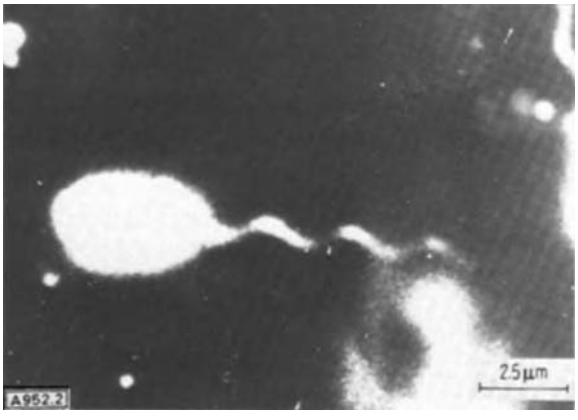

Fig. 2. Photomicrograph of a Salmonella bacterium with its bundle of normal flagella during locomotion (dark field illumination). The photograph was kindly supplied by *Dr. T. Iino* and *Dr. S. Asakura.*

bundle of flagella always points in the opposite direction to the motion. Helical waves continuously run along the bundle in the distal direction, with the result that the bundle assumes the appearance of a rotating helix. At the same time the body of the bacterium appears to move forward in the medium with a helical motion in the opposite direction. Some bacteria can reach speeds of 50 μm/s in this way, *i. e.* they can cover many times their own body length in one second.

When the bacteria are executing slow swimming movements it is sometimes possible to observe transitions of the bundle between two different helical shapes, corresponding respectively to a normal helix and to a helix with only half of the normal pitch (curly type)[10]. This ability of the bundle of flagella to occur successively or simultaneously in two definite, clearly distinguishable helical forms is known as biplicity. Since such transitions can be observed only relatively rarely during movement, however, they cannot be necessary to or responsible for the locomotion.

3. The Fine Structure of the Flagella

Whereas the flagella can be broken off at the cell wall by mechanical treatment, *e. g.* shaking, stirring, or centrifugation, whole flagella can be prepared (including anchoring) and investigated by mild enzymatic detachment of the cell wall and treatment with detergents[13, 14]. According to these investigations, all bacterial flagella, regardless of their source, consist of three morphologically distinguishable parts. The flagellum begins in a *basal body* connected to the cytoplasmic membrane, passes through the cell wall with the *flagellar hook*, and then continues in the long helical *main filament*.

It has only recently become possible to recognize fine structures in the isolated basal region[13]. It has been found that in gram-negative bacteria such as *E. coli*, there are four circular discs offset from one another on a relatively thin pin. In the inserted flagellum, three of the rings are probably each joined to one of the definite layers of the cell capsule of gram-negative bacteria, *i. e.* the cytoplasmic membrane (inside), the murein layer (center), and the lipopolysaccharide layer (outside)[13]. The connecting element between the basal body and the helical main filament is the flagellar hook, a slightly curved cylinder about 500 Å long (see Fig. 3). Its diameter is usually slightly greater than that of the filament, from which it also differs in its greater temperature resistance and its greater resistance to deaggregating agents[4, 13, 14]. It apparently consists of a protein different from that of the main filament[4, 14].

Fig. 3. Electron micrograph of a separated flagellum of *Proteus mirabilis* with hook and incised "tail end" (cf. text) after negative staining with 2% potassium tungstophosphate solution at pH 7.

Connected to the flagellar hook (often *via* a slightly narrower region) is the helical main filament; this part alone is often referred to as the flagellum. With a few exceptions, in which another protein envelops the filament in a flagellar sheath[4, 15], the flagella consist of chemically identical structural units of a single protein, flagellin. According to electron micrographs, egg-shaped morphological subunits, which according to their dimensions of about 50 Å[15, 16] must be identical with flagellin, form a cylinder (Fig. 4). In some cases the subunits appear to be roughly hexagonally packed, and a distinct oblique striation indicates a helical arrangement of the protomer strands (A

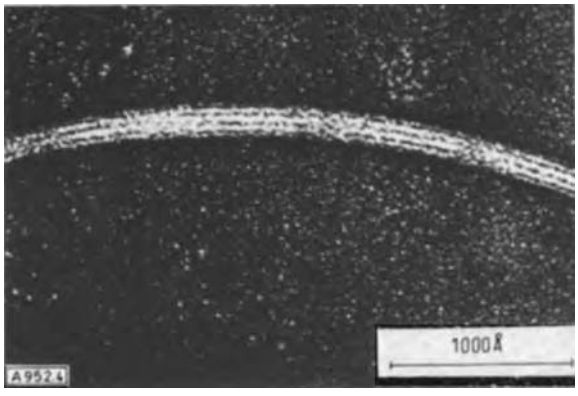

Fig. 4. Flagellum (B form) of *Pseudomonas fluorescens* with periodically disturbed longitudinal stripe pattern. The photograph (staining with uranyl acetate) was kindly supplied by Dr. *J. Lowy*.

form[15]). In other cases (Fig. 4) the cylinder wall appears to consist of eight[15], nine to ten[17, 18], or eleven[19, 20] longitudinal flagellin rows (B form[15]).

Very accurate determination of the distances between the subunits in the axial direction from electron micrographs and from X-ray fiber diagrams gave a value of 52 Å[21–23], while the lateral distances between the longitudinal rows or subunits were found to be 40 to 60 Å[4, 15, 16]. The distances in the axial direction, unlike those in the lateral direction, were found to be extremely resistant to variation with the degree of drying and the contrasting and preparation method[24].

Negative stain such as potassium tungstophosphate can deposit in the axial region of flagella that have been shaken off, particularly after shortening by ultrasound or by repeated freezing and thawing (Fig. 5). In this way contrast

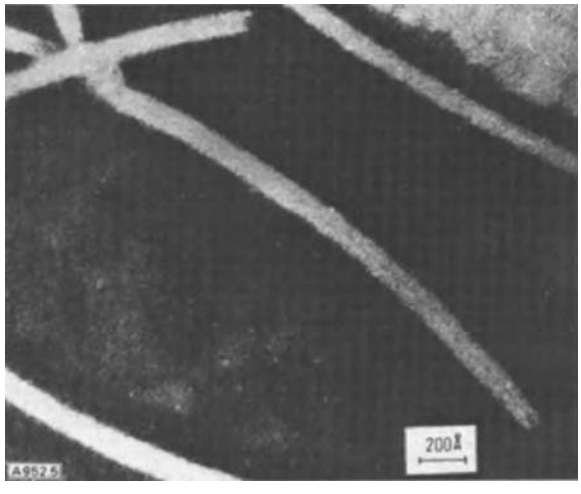

Fig. 5. Electron micrograph of flagella (*Proteus mirabilis*) treated with ultrasound, after negative staining with 2% potassium tungstophosphate solution at pH 7. A weak black central line is visible.

lines up to 30 Å thick can appear in the axis of short flagella[4, 16–18], but these are never so clearly visible as *e. g.* in the tobacco mosaic virus or in bacteriophage tails[15]. X-ray diffraction studies on oriented bundles of flagella[25] and small-angle X-ray measurements on flagella of various lengths in solution[17, 18] also indicate the presence of a hollow central channel. In the latter case the

flagella of *Proteus mirabilis* exhibit roughly the same scattering as a long hollow cylinder having an outside diameter of 150 Å and an inside diameter of 30 Å[18].

Differently formed ends can be observed in certain cases on short fragments of flagella[4, 10, 17, 18, 26, 27]. After negative staining one end is always round to pointed, while the other has an incised appearance (Fig. 6). After shadowing with heavy metal, on the other hand, only the tip is visible, while the "tail end" has disappeared[28]. As can be seen from Figure 3, this incision is situated at the distal end of the anchored flagellum, *i.e.* the end remote from the bacterial cell and the flagellar hook.

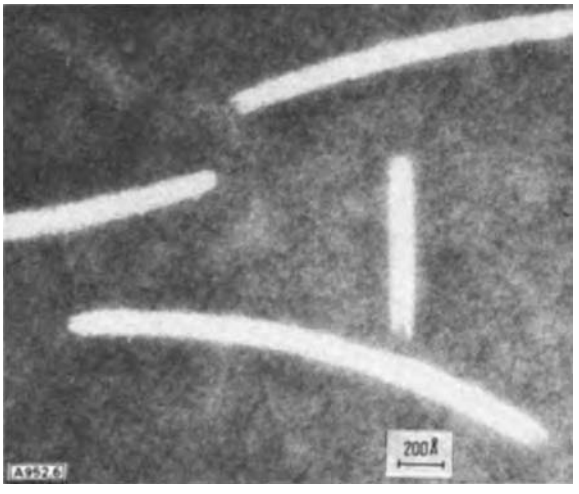

Fig. 6. Electron micrograph of flagella *(Proteus mirabilis)* treated with ultrasound, after negative staining with 2% potassium tungstophosphate solution at pH 7. A round to pointed end and an incised end are visible.

Enough observations have now been reported to enable us to build up a fairly detailed model of the fine structure of the flagellar filament. In the construction of this model we shall make use of yet another piece of information, which we cannot substantiate in full until Section 4. This is that the flagellin monomer is not spherical in shape, as was formerly assumed[15], but is a highly elongated molecule[17, 18]. Since cylindrical close packing of long protomers is possible only if each subunit is less voluminous close to the axis of the cylinder than at the periphery, a wedge should be a reasonable approximation to the actual shape of the protomer. Following *Lowy* and *Hanson*[15] it has been assumed in the fine structure model (Fig. 7) that (in the flagella of Eubacteriales) the flagellin protomers are lined up at regular intervals of 52 Å in eight roughly axially parallel strands, which in turn are combined to form a hollow cylinder. At the same time the protomers in neighboring lines are displaced and arranged hexagonally, and form helices with eight subunits per turn.

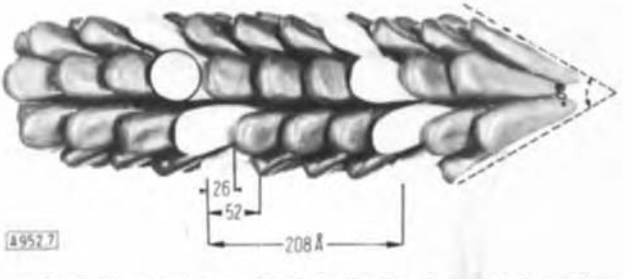

Fig. 7. Fine-structure model of the flagellar filament, built up from wedge-shaped subunits [18] (for explanation see text).

One of these four identical 8/4 helices is shown in Figure 7 with light coloring for better visibility. The helical surface lattice is defined by the crossing of the (four) 8/4 helices and the (eight) longitudinal lines (generally by two families of parallel helices). The exact arrangement of the protomers and the number of longitudinal lines (according to the latest measurements by optical diffraction[19, 20], nearer to eleven than to eight) are not definitely known at present. According to this model[18] the explanation of the morphological subunits, which appear in electron micrographs to be roughly round with a diameter of about 50 Å, is that only a small circular part of the elongated protomers can be seen on the surface.

With its conical end and its incised end, this model can also explain, on the molecular level, the different end structures of the polar flagella (Fig. 6). In contrast with the large axial channel with an effective diameter of about 60 Å in the Lowy-Hanson model, the protomers in this fine-structure model leave only a narrow free channel with a diameter of about 30 Å, as indicated by the X-ray measurements and the relatively weak stainability (Fig. 5).

4. Flagellin

On treatment with detergents, structure-disrupting salts[17], acids[29, 30], or alkalis, or on heating[31], the helical filament breaks down into identical flagellin subunits, which are therefore linked only by non-covalent bonds in the flagellum. Monomeric flagellin is usually prepared by thermal or acid-induced dissociation (cf. Ref. [4]). In the ultracentrifuge under physiological conditions (pH = 7, approx. 0.15 mol of NaCl/l), the molecular weight of flagellins from various organisms has been found to be about 40000[18, 29–33]. This value has been confirmed in denaturing reagents such as 6 M guanidinium hydrochloride, by sodium dodecyl sulfate disc-electrophoresis, or by analysis of the flagellin peptides after cleavage with trypsin or BrCN[18, 34–37].

It was thus also shown that in most cases flagellin is the only protomer, and the smallest protomer of the flagella and consists of a single peptide chain. However, two chemically very similar but distinguishable protein components have been found in the flagella of a few organisms[4]. It is not yet possible to decide whether this is due to a macroheterogeneity or to a microheterogeneity of the material examined[4]. In some Salmonella bacteria, however, two structural genes for the biosynthesis of flagellin have been found to occur together, one of these becoming active and the other inactive according to the phase (cf. Refs. [4, 9]).

The carbohydrate component that is sometimes detected in small quantities in flagellin preparations is probably due in most cases to contamination with cell-wall polysaccharides, which, in contradistinction to the H antigens of the flagella, are the bacterial O antigens[38]. All flagellins

have a characteristic amino acid composition. They never contain cysteine or tryptophan, they rarely contain proline or histidine, and they usually contain little methionine, tyrosine, and phenylalanine. Another striking feature is a relatively high content of nonpolar, hydrophobic amino acids. The rare amino acid ε-*N*-methyllysine has been found in some flagella[4, 34, 36]. A number of lysines localized in certain regions of the peptide chain are presumably methylated enzymatically in the completed flagellin molecule[36]. Immotile mutants with perfectly straight flagella have been produced from a wild type of *Bacillus subtilis* having normal helical flagella by treatment with mutagenic reagents[39, 40]. In every case the mutation resulted in the identical single amino acid substitution, *i.e.* in replacement of the original alanine by valine.

It is possible (cf. Section 5) to keep flagellin in solution in the monodisperse state for long times in neutral buffers[18, 29, 31]. This allows the measurement of shape and structure parameters of the flagellin. The radius of gyration and the Stokes radius of the isolated flagellin of *Proteus mirabilis* in neutral solution have been measured in this way (by X-ray small angle scattering and from its elution behavior on Sephadex gels), and were found to be about 40 and 37 Å respectively[17, 18]. For comparison, the radius of gyration and the radius of a compact sphere having the molecular weight and partial specific volume of flagellin would be only 17.5 and 23 Å respectively.

The sedimentation constant s is also very much smaller and the viscosity number $[\eta]$ larger than one would expect for a spherical solvated particle. Flagellin thus behaves hydrodynamically as an elongated rigid ellipsoid of revolution with an axial ratio of about 9:1[18]. Flagellin gives roughly the same scattering as a row of elongated geometric bodies having a somewhat smaller axial ratio and an average length of about 160 Å. On the assumption that the shape of the isolated flagellin is not very different from that of the polymerized flagellin, the fine-structure model was constructed from such equivalent scattering and wedge-shaped subunits (Fig. 7)[18].

It has been shown by optical rotatory dispersion (ORD) and circular dichroism (CD), two optical methods that yield information on the content of secondary structures in proteins, that at roughly physiological pH values and salt concentrations and at room temperature, the conformational and structural states of the isolated flagellin are independent of its previous treatment[18, 27, 41–44]. From its molar ellipticity of -8800 degrees·cm^2/decimol per mean amino acid residue at 220 nm, the content of α-helical structural regions in the flagellin of *Proteus mirabilis*[45] can be estimated by the usual methods to be about 25% (cf. other values in Refs. [4, 41–44]).

5. The *in vitro* Reaggregation

Flagellin can reaggregate *in vitro* to form long helical filaments that are practically indistinguishable from the original native flagella on examination in the electron microscope, from their X-ray diffraction pattern, or from their optical properties. This self-organization process is sometimes referred to as polymerization, though it does not involve the formation of covalent bonds. The flagellin from *Bacillus pumilus*, for example, polymerizes relatively rapidly in 0.02 M phosphate buffer between pH 5.4 and 5.6 (the isoelectric point of the flagellins is around 5) at 26 °C to form flagella-like filaments. Between pH 4 and 4.9, on the other hand, it forms linear structures, which are also converted irreversibly into helical filaments when the pH is raised[30]. Flagellin also polymerizes spontaneously in semiconcentrated neutral solutions of certain "salting-out" anions (*e.g.* CO_3^{2-}, F^-, SO_4^{2-}, HPO_4^{2-}) [10, 46, 47]. In this "salt polymerization", the formation rate and the number of fragments increase with the concentrations of flagellin and of salt in a molarity range between 0.4 and 1.2, while the length of the filaments ultimately formed decreases. From the concentration dependence of the length and formation rate of the filaments it has been estimated that about three monomers must come together for nucleation[10, 47].

Around pH 7 and in the presence of about 0.15 mol/l of sodium chloride, flagellin solutions remain monodisperse and stable for long periods, and detailed investigations can therefore be carried out on dissolved native flagellin (cf. Section 4). In the presence of flagella fragments (seeds) about 0.3 μm long, which can be prepared by ultrasonic treatment, on the other hand, the flagellin monomers polymerize relatively rapidly on these seeds under these conditions[31]. In this "seed polymerization" the fragments grow exclusively at the tail end (cf. Fig. 6)[27]. The polymerization rate is directly proportional to the number of seeds added. It increases with increasing monomer concentration up to a limiting or saturation value of about 15 mg of flagellin/ml, when the time between the incorporation of two monomers is about 0.3 s[10].

The stability of the flagella and the ability of flagellin to undergo seed polymerization show that the isolated flagellin in 0.15 M sodium chloride solution at about pH 7 and at room temperature is in a kinetically inhibited state; only the helical filaments are thermodynamically stable under these physiological conditions. Thus while seed formation is extremely slow and difficult, relatively fast chain growth occurs in the presence of seeds added as such or spontaneously formed in another solvent. Like *e.g.* the G-F actin system[48, 49], therefore, this flagella-flagellin system exhibits characteristic properties of a cooperative aggregation, such as are observed *e.g.* in crystallization or other phase transitions[50, 51].

In the theory of linear (or helical) cooperative aggregations[48, 50–52] it is assumed in the simplest case that above a certain nucleus size, all subsequent elementary equilibrium growth steps can be described by the same equilibrium constant K. Only the first nucleation steps should be thermodynamically less favorable, since the rate constants of the nucleation may be very much smaller than those of the elongation of the seed. This may be so *e.g.* because the monomers taking part must change their conformation together before or during the seed formation (see below) or because there are fewer bonding sites available per monomer in the seed than in the larger aggregates (cf. Ref. [48]). Though the smallest stable nucleus may

be a higher oligomer (see above), the more difficult nucleation step will be taken here as dimerization, with the dimerization constant $K_2 = \sigma \cdot K$ (after *Winklmair*[53]). The more the monomer needs the seed as a conformation or growth matrix, the smaller is the cooperativity parameter σ. The precise state of such a monomer-polymer equilibrium system then depends on σ and K (and hence on external parameters such as the pH, ionic strength, nature of the salts, temperature) and on the total protomer concentration c_t, since the reactions involved are bimolecular. In the case of very high cooperativity ($\sigma \ll 1$), the solution at $K \cdot c_t < 1$ contains almost exclusively monomer, whereas at $K \cdot c_t = 1$, *i. e.* at the critical micelle concentration $c_t = 1/K$, polymer suddenly also appears[48,53].

It has unfortunately not yet been possible to carry out true equilibrium measurements on flagellin (unlike in the case of actin[49]) to test the theory, since the association takes place extremely slowly close to equilibrium and the true equilibrium is therefore difficult to determine. In one case, however, there is a report of a "critical flagellin concentration" for Salmonella flagellin[10]. Thus it was observed viscometrically that at 40 °C, seeds depolymerized in solutions with flagellin concentrations of less than 0.6 mg/ml, whereas they were stable at a flagellin concentration of 0.6 mg/ml, and grew at the expense of the monomeric flagellin at higher concentrations. However, there is certainly no physically uniform flagellin species present at the experimental temperature of 40 °C. Thus with rising temperature the α-helical component of flagellin decreases rapidly above 27 °C[18] or 35 °C[41]. Dilatometric studies have also shown a change in the structure of unfolding of flagellin in this temperature range. During the polymerization of flagellin, the molar volume changes by +150 ml/mol of flagellin below 28 °C, and by twice this value above 35 °C[54]. The polymerization rate increases with rising temperature below 27 °C, but decreases again above this temperature[17,30,54]. In a semilogarithmic plot of the initial polymerization rate[17] or of the half life of the polymerization[54] against the reciprocal of the temperature, the Arrhenius activation energy of the growth step was found from the slope of the linear graph (between 4 and 20 °C) to be 8 to 10 kcal/mol. Apparently negative activation energies are found at higher temperatures because of the negative temperature coefficient of the polymerization rate (see above). Attempts have been made to explain this by a strongly temperature-dependent reversible pre-equilibrium between active and inactive forms of the monomer[17,54].

The CD and ORD spectra of flagella are similar to the spectra of flagellin, apart from a slight red shift[42,45]. However, the molar ellipticity per mean residue of the flagella at 220 nm, with a value of about −15000 degrees cm²/decimol[44,45], is 1.7 and 1.5 times the value for isolated flagellin in physiological buffers and in polymerization-promoting 0.9 M ammonium sulfate solution respectively[44,45]. This marked increase in the optical activity during polymerization is often interpreted as evidence of a conformational change that the monomer must undergo before, during, or after incorporation into the flagellum[4,10]. Without quantitative calculations or measurements in systems of similar complexity, however, it is difficult to estimate the extent to which the helical arrangement and close packing of the optically active protomers in the flagellum (see Fig. 7) can influence or increase the rotational strength of the electronic transitions (cf. cholesterol phases[55]). The particle scattering, which has been discussed and measured for very large optically active particles[56,57], does not appear to be the cause of these optical effects[10,44], particularly since this should in fact lead to smaller amplitudes (but cf. Ref. [4]).

The Salmonella and Proteus flagellins, with about 380 amino acid residues, have arginine at the carboxyl end[34,36,58]. After enzymatic cleavage with carboxypeptidase B the flagellin largely loses its ability to undergo spontaneous and rapid polymerization *in vitro*[45,58]. In the flagellum, on the other hand, this C-terminal arginine is resistant to enzymatic attack. The carboxyl terminus must therefore be localized in or near the contact surfaces between the flagellin protomers. Most of the tyrosine and methionine residues (5 to 10 and 2 to 10 respectively, depending on the flagellin species) are presumably also situated at the protomer bonding surfaces, since they are accessible to typical modification reagents or to hydroxide ions in the isolated flagellin, but not in the polymeric flagellum[4,17,36,43,59]. A particularly large number of apolar amino acids must also be involved in the intermolecular bonds, the content of such amino acids in flagellin being unusually high (see Section 4).

Typical indications of such hydrophobic bonds, in addition to weakly positive molar reaction enthalpies ΔH and strongly positive changes in molar volume ΔV, are strongly positive values for the molar reaction entropy ΔS. On association of peptide monomers, the number of contacts between hydrophobic groups and surrounding water molecules decreases, with the result that the latter gain increased freedom of movement. The resulting positive reaction entropy in particular favors the protein aggregation in accordance with the fundamental thermodynamic relation between ΔH and ΔS on the one hand and the molar free enthalpy of reaction ΔG on the other ($\Delta G = \Delta H - T\Delta S$)[60,61]. The considerable increase in the molar volume on polymerization of flagellin (see above) is also an indication of the participation of such hydrophobic intermolecular interactions in the flagellum. Calorimetric studies being carried out at present[62] will show how far this is supported by the enthalpy and entropy effects.

6. The Polymorphism

As was mentioned in Section 2, flagella with polymorphous helical forms have been found in bacteria, these forms being referred to as normal (n), short-wave or curly (c), and straight (s) (see Fig. 8). *Asakura et al.* have investigated the properties of flagellins that decide the flagella form or that are responsible for conformational adaptation by seed polymerization experiments with uniform or mixed solutions of n, c, and s flagellins[10,33,63]. On polymerization of a small quantity of n or c flagellin with many long c or n seeds, the newly grown piece of filament assumed the curly form in both cases. In solutions containing very

large quantities of n, c, or s flagellin together with a few short seeds (regardless of type), on the other hand, the form of the polymerizing filaments was largely determined by the nature of the monomer[33].

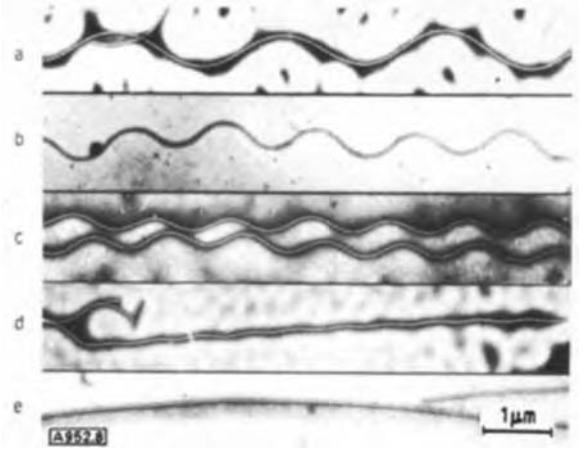

Fig. 8. Electron micrographs of the five stable types of filaments, obtained by copolymerization of n and s flagellins [10] in the ratios: a) 1:0 (normal (n), type I); b) 9:1 (type II); c) 1:1 (curly (c), type III); d) 1:9 (type IV); e) 0:1 (straight (s), type V). The photographs were kindly supplied by *Dr. S. Asakura*.

The filaments formed in this way were measured under the electron microscope and characterized by the contour length L per one wavelength λ and by their maximum wave height h. In the mixed polymerization of n and s flagellins, after the addition of a very small number of short seeds, five clearly distinguishable filament forms are observed, depending on the mixing ratio (cf. Fig. 8 and Table 1); whereas homogeneous solutions of n or

Table 1. Shape parameters of the filaments obtained by copolymerization of n and s flagellins (after [10], cf. text and Fig. 8).

	Type				
	I	II	III	IV	V
Contour length L [µm]	2.70	1.54	1.15	0.63	0
Wavelength λ [µm]	2.49	1.36	1.08	—	0
Wave height h [µm]	0.45	0.31	0.16	0.027	0

of s flagellin gave almost exclusively filaments of normal wavelength (Fig. 8a, type I) or straight filaments (Fig. 8e, type V), mixed solutions (n + s) gave three other undulating (helical) types of filaments II, III, and IV (Fig. 8b, 8c, and 8d). Since the wavelength and the contour length decrease with increasing content of s flagellin, the perfectly straight s flagella correspond to the limiting case of infinitely small L and λ values[10]. Similarly, the copolymerization of c and n flagellins gave, in addition to normal flagella, two shortwave types of filaments resembling types II and III (Fig. 8 and Table 1), depending on the mixing ratio[10,63].

It is interesting to note that the filaments formed by copolymerization were nearly always of the same form throughout, though because of their different polymerization rates the various types of flagellin were not quite uniformly distributed in the filaments. On rare occasions, under certain external conditions, reversible transformations between the n and the c forms were observed for filaments of pure n flagellin; in every case, the filaments as a whole assumed one of these forms[33] ("all-or none" case[61]). Apparently, therefore, it is energetically most favorable for the filaments to be of a uniform type over their entire length. Each flagellin species can be incorporated into several stable types of flagella. As their content in the mixture increases, however, the flagellins increasingly impose their preferred form on the filaments (see Fig. 8).

7. The *in vivo* Growth

Motile bacteria can develop complete flagella about 10 µm long within at most a few generations[4]. Under favorable growth conditions, for example, Salmonella bacteria can lengthen their flagella by about 0.15 µm/min at 37 °C[4,64]. It was mentioned in Section 5 that in seed polymerization *in vitro*, flagellin adds exclusively to the incised tail ends of the filaments (see Figs. 3 and 6). It has recently been shown by two elegant experiments that the *in vivo* growth of the flagella also takes place at the incised distal end, *i.e.* at the end remote from the bacterial cell. In the first experiment, use was made of the observation that certain normal strains in a complete medium containing *p*-fluorophenylalanine instead of phenylalanine produce only curly flagella instead of the normal flagella[65]. When the bacteria were transferred from a normal culture medium into one containing *p*-fluorophenylalanine, the growing flagella suddenly became curly in their distal regions. These regions must therefore have been synthesized last[66]. This surprising result has recently been confirmed by autoradiographic studies, in which the bacteria were incubated during their growth phase first in a cold medium and then in a tritium-labeled medium[66]. Evaluation in the electron microscope showed that film was blackened mainly by the parts of the filaments remote from the flagellar hook; these were therefore the labeled parts, and must have been formed last.

It is not yet known how the flagellin protomers are transported from the cell body to the often very distant growth zones of the flagella *in vivo*. In another experiment[67] the straight s flagella of immotile mutants were shortened by ultrasonic treatment, and relatively concentrated solutions of n flagellin were then added. After a time, actively motile bacteria were observed in the solution, some having heteromorphous flagella with a straight proximal part and a normal distal part, but most with completely normal flagella. The added n-flagellin must therefore have been polymerized from the solution onto the stumps of the flagella. It is almost certain, however, that the natural formation of flagella does not involve secretion by the cell of free dissolved flagellin into the open surrounding medium followed by growth after the fashion of seed polymerization, since free flagellin has never been detected in bacteria suspensions outside the cells. Moreover, the high *in vivo* growth rate observed at 37 °C was measurable *in vitro* only at room temperature and with relatively high

flagellin concentrations (approx. 5—10 mg/ml)[10,33] (cf. Section 5); the incorporation mechanisms *in vivo* and *in vitro* are therefore presumably different. It must be assumed that after its biosynthesis at the basal membrane[4] the flagellin is released into the flagellum channel detected by various workers (Section 3 and Fig. 5), where it "diffuses" actively or passively, according to the concentration gradient, to the distal end of the flagellum, and is incorporated directly there.

8. The Helix Form

In the fine structure model (Fig. 7), which should demonstrate among other things the probable short-range order within a short piece of filament, the flagellum filament is treated as a straight rod similar to the tobacco mosaic virus or the bacterial pili[1]. As described earlier (Section 2), however, most flagella are twisted into a helix both in the functional state and in the isolated state. Simple symmetry considerations show that because of the superhelical structure of the flagella the positions occupied by the individual, chemically identical flagellin subunits cannot be completely identical but since the proximity relations are only similar may occupy only quasi-equivalent positions in the flagellum[68]. This should also be taken into account in a refined flagella model that is nevertheless as simple as possible.

Klug[68] assumes two sets of protomer bonds with roughly equivalent energies, either of which alone leads to straight, easily distinguishable cylinders. Simultaneous (partial) saturation of both sets of bonds in a structure, on the other hand, is possible only in a cylinder whose axis is deformed into a helix. It will be shown below with the aid of another model how a tube consisting of many very similar structural units can assume several distinguishable superhelical forms according to the arrangement of these units. Following a suggestion by *Asakura*[10] it is assumed that the subunits can occur essentially in only two distinguishable forms (conformations) in the superhelix (flagella helix).

When the planar regular surface lattice[69] (Fig. 9a) is rolled up, one obtains the lateral surface of a straight cylinder (Fig. 9b), in which, by analogy with the fine-structure model (Fig. 7), subunits with schematized square cross sections are arranged in eight axially parallel lines (A to H). For simplicity, the subunits or protomers in neighboring lines are not shown displaced in relation to one another. They are completely identical or equivalent in their form and, apart from the two arbitrarily chosen ends, in their position and proximity relation.

Fig. 9. a) Surface lattice, and b) corresponding cylinder model.

Let us now consider the case in which all the protomers of one of the artibrarily chosen longitudinal lines (*e.g.* E) assume a somewhat longer and simultaneously angled form. The protomers of the other lines should try to preserve the original (shorter and square) form with retention of a closed tube surface; this is best achieved by the A line, which is furthest away from the E line. The corresponding planar surface lattice is shown in Figure 10a. The

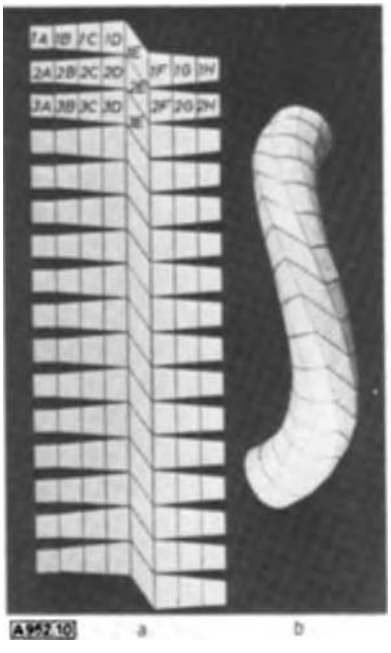

Fig. 10. a) Surface lattice, and b) corresponding superhelix model: for relations between Figures 9a and 10a see text.

introduction of the new type of protomer has the following consequences: its angled form leads to a displacement in the individual numbered transverse lines, so that these and also the longitudinal lines are no longer perpendicular to and parallel to the axis of the cylinder when the lattice is rolled up (Fig. 10a), but are oblique to the axis (Fig. 10b). At the same time, the cylinder will roll up because of the differences in length of the "longitudinal" lines. Since the longest (shortest) line of protomers always tries to lie along the outer, longer, (inner, shorter) line of curvature, the cylinder, because of their oblique course, does not become a torus, but is deformed into a large helix (Fig. 10b). The parameters of the helix are conclusively given by the displacement and the differences in size of the subunits. However, these now have only similar proximity relations, and their shapes and contact surfaces even in the central sections of the tube are no longer exactly identical, but are only quasi-equivalent.

If the protomers of another neighboring line (*e.g.* D in Figure 11a) now assume the longer angled form, an even tighter helix with a smaller pitch and a smaller diameter will be formed (Fig. 11b), and so on. Finally, if all the lines are transformed, because of the identity of the subunits, regardless of their (uniform) shape and size, one again obtains a straight cylinder (Fig. 12b), whose "longitudinal" lines A—H make a greater angle with the axis of the tube than those of any other cylinder or superhelix, and whose dimensions are different from those of the original straight cylinder (Fig. 9b).

For simplicity, the square arrangement of the protomers has been chosen in this model instead of the hexagonal arrangement found in the flagella (cf. Section 3 and Fig. 7). However, the latter could be introduced with no fundamental changes by mutual displacement of the "longitudinal" lines. This simple model now offers a plausible explanation for the polymorphism and the biplicity of the flagella. It shows how with a single protomer species, which can exist in only two forms (conformations), it is possible to build up several helical structures as well as cylindrical structures, depending on the occupation ratio, these helical structures differing from one another in contour length L, in pitch λ, and in the diameter of the helix (roughly equal to h).

In the superhelix models (Figs. 10 and 11), the "longitudinal" lines A to H include one or two longer than the others (D, E), one or two shorter than the others (A, B), and several lines of intermediate length, which run round the tube in large spirals (long-range helix). These spiral lines presumably correspond to the "longitudinal" flagellin lines (Fig. 7), which are probably not parallel to the axis of the filament, but inclined to it *e.g.* at an angle of 1 to 2° in the normal helical flagella[7]. The periodic disturbances in the longitudinal stripe pattern of negatively

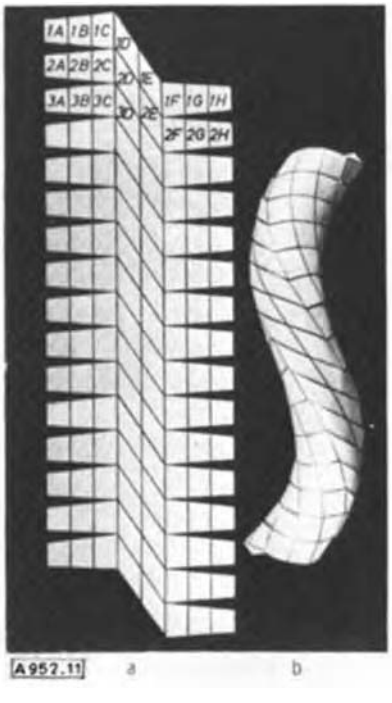

Fig. 11. a) Surface lattice, and b) corresponding superhelix model; for relations between Figures 11a and 10a see text.

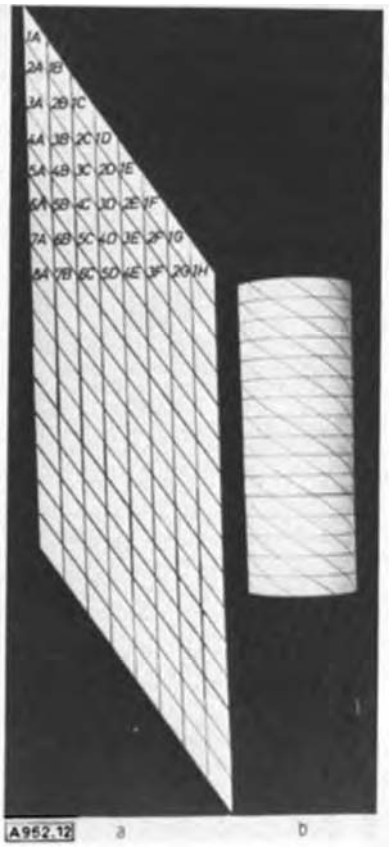

Fig. 12. a) Surface lattice, and b) corresponding cylinder model; for relations between Figures 12a and 11a see text.

stained flagella (see Fig. 4) have been satisfactorily explained as resulting from the superposition of the protomer strands on the upper and lower sides of the flagella, which form an acute angle with one another[7].

It has recently been shown by optical diffraction and optical filtering on electron micrographs of straight flagella that the (eleven[19]) protomer lines in straight flagella run at the fairly large angle of about 7° to the axis of the flagellum[19] (cf. Fig. 10d). For the sake of clarity the size relationships have been completely distorted in the models (Figs. 9 to 12). Thus the calculated number of protomers per turn of the helix is 4000 for normal flagella, whose helix diameter of 3400 Å[10,70] is many times their tube diameter of about 150 Å. Moreover, the protomers of the longest (outer) and of the shortest (inner) lines differ by only 1 to 2% in the n flagella. Because of this small, systematic variation in the regular bonding pattern (which is the definition of quasi-equivalence[68]) the c and n flagella acquire a helical structure that is evidently very much more stable than straight cylinders (with an equivalent arrangement of the protomers). Since the flagella are mostly in a uniform helical form, very strong cooperative proximity interactions must exist between the individual protomers[50].

9. The Movement of the Flagella

The model described above also provides a useful hypothesis for the manner in which motion occurs within the

flagellar filament. Since the filament evidently possesses no ATPase activity, it must be assumed to serve purely as a passive conductor of a helical wave motion induced by chemical energy in the basal region[68]. This requires a high cooperativity not only within the "longitudinal" lines, but also (*via* the hook portion) between these lines and the corresponding structures in the basal region. These structures could determine the conformations of the individual lines, so to speak, as allosteric effectors[71] (cf. end effects in linear biopolymers[50]). If *e.g.* the individual lines in the helical models (Figs. 10 and 11) were forced in cyclic succession into the longer angled structure, these lines would strive in turn to position themselves on the "outside" of the superhelix. The helical filament could thus pass through several microscopically indistinguishable and energetically fully equivalent (degenerate) microscopic states, which are presumably separated from one another only by low activation barriers (this is also indicated by the polymorphism). In this way undamped helical waves could travel along the flagellum to the tip[6, 7, 68], in agreement with observations on flagellar bundles (Section 2). This process would also lead to an apparent rotation of the helical filaments in relation to the base[5, 7, 72], the individual protomers retaining their orientation in space during the motion. Unlike a free rope with a plane wave traveling along it, however, a free helix could not produce a forward thrust by such a rotation; because of the conservation of angular momentum it would appear to be stationary[5]. Attachment to the large bacterial cell bodies prevents this free rotation and, on the contrary, allows by rotation, at different speeds, of the flagella on the one hand and of the cell body on the other, the production of a forward thrust[5, 6] that is sufficient, according to calculations, to propel the organisms at the observed speeds of up to 50 μm/s. This involves only viscous forces and not *e.g.* inertial forces[6].

In the author's opinion the flagellar hook (Section 3) plays an important part in connection with the structure and function of the filament. It is thought that the filament arises perpendicularly from the membrane and passes perpendicularly through the cell wall, and that only then does it assume the helical curvature. The curvature of the flagellar hook, which is assumed to be planar, could fulfill this function very satisfactorily. In the (apparently) rotating helix, the protomer line that is outermost in the helical part, *i.e.* that forms the longest helical line, should always be shortened in the hook; in other words, its structural and functional pattern should be exactly reversed. If the hook, which is situated outside the cell, is essential to the structure and function of the flagella, it must also be the first part to be formed if short flagella that are not yet complete are to be capable of functioning. This could be one reason for the unique fact that the flagella grow at their tips (Section 7).

10. Outlook

It must be pointed out that it was frequently necessary to use hypotheses in the foregoing discussion. Very many questions still remain unanswered, examples being those of the position and nature of the flagellin biosynthesis and the conversion of chemical energy into mechanical energy. The initiation, control, and coordination of the movement of the flagella is naturally still a complete mystery. One is inclined to localize this function in the basal region and the adjoining cell membrane. This must also be the seat of conduction mechanisms between the detect able chemoreceptors[73] and the motion centers, which are essential to the chemotactic and phototactic behavior of many bacteria, *i. e.* their ability to respond to nutrient gradients or light gradients by controlled reflexes[74]. The apparently simple bacterial locomotion organelles thus in reality form an extremely complicated structural and functional chain, about whose individual links little is known as yet. In the helical flagellar filament, nature may have presented us with a relatively simple structure that shows in exemplary fashion how information can be transmitted in the cell *via* linear or two-dimensional (membranous) protein aggregates by non-electrical means, *i. e.* by cooperative interactions in allosteric protein structures. At all events, structures similar to that of the flagellar tube have been found in mechanoreceptors, chemoreceptors, and photoreceptors[75–78].

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Zintl Phases: Transitions between Metallic and Ionic Bonding

By Herbert Schäfer, Brigitte Eisenmann, and Wiking Müller[*]

Experimental studies on compounds of alkali and alkaline earth metals with semi- and metametals have considerably broadened the basis for a discussion of the transition from metallic to ionic bonding. Current interest is focused mainly upon the elucidation of the principles governing the structure of such compounds which are subject to a wide range of variation within this class of materials. A new definition of the term Zintl phase is proposed after consideration of available findings.

1. Introduction

Pauling and *Mulliken* have shown that the bonding in certain classes of inorganic compounds can be regarded as a transition from atomic to ionic bonding. Introduction of the electronegativity concept enabled chemists to describe the transition atomic bonding—ionic bonding and to correlate numerous individual observations.

No such considerations have been made for the transition from atomic bonding to metallic bonding. The first step in this direction is found in *Pauling*'s views on the metallic bond. Studies on complexes having direct metal-metal bonds by X-ray and magnetic methods have revealed interesting new facts. However, these have also failed to indicate new general guidelines so far.

The transition from metallic bonding to ionic bonding is only poorly characterized owing to a long period of comparative neglect. Although efforts were repeatedly made to incorporate ionic bonding contributions into descriptions of bonding even in early publications on metals and alloys, a systematic study of this transition was thwarted by experimental and methodological problems posed by the most suitable systems. In recent years its study has resulted in a broader knowledge of inorganic compounds and opened up new aspects in treatments of bonding in intermetallic phases, which is attracting increasing interest on the part of modern bond theory.

Table 1. Compounds of lithium with elements of Group IIIB—VIIB. Formulas in italics refer to compounds of known structures.

III	IV	V	VI	VII
Li_3Al [30] *Li_9Al_4* [31] *LiAl* [32] Li_2Al_3 (cited in [33])	*$Li_{22}Si_5$* [9, 10] Li_4Si [11] *Li_7Si_2* [12] *$Li_{10}Si_3$* [13] *Li_2Si* [14] $Li_{13}Si_7$ [11]	*Li_3P* [4] Li_2P [5] LiP [6] *LiP_5* [238] *LiP_7* [238]	*Li_2S* [3]	*LiCl* [2]
Li_2Ga [33] or Li_9Ga_4 *LiGa* [34]	*$Li_{22}Ge_5$* [9] *$Li_{15}Ge_4$* [15, 16] *Li_7Ge_2* [17] Li_3Ge [18, 19] *Li_9Ge_4* [20] *LiGe* [21, 22]	*Li_3As* [4] *LiAs* [7]	*Li_2Se* [3]	*LiBr* [2]
$Li_{20}In$ [33] Li_9In [33] Li_9In_2 [33] Li_4In [33] Li_3In [33] Li_9In_4 [33] Li_3In_2 [33] *LiIn* [34]	*$Li_{22}Sn_5$* [9] Li_4Sn [23] Li_7Sn_2 [23] Li_5Sn_2 [23] Li_2Sn [23] *LiSn* [25] $LiSn_2$ [23] *Li_2Sn_5* [24]	*Li_3Sb* [4]	*Li_2Te* [3]	*LiI* [2]
Li_4Tl [35] Li_3Tl [35] Li_5Tl_2 [35] Li_2Tl [35] *LiTl* [34]	*$Li_{22}Pb_5$* [26] *Li_7Pb_2* [27] *Li_3Pb* [27] *Li_8Pb_3* [27] *LiPb* [28, 29]	*Li_3Bi* [8] *LiBi* [8]		

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Table 2. Compounds of sodium with elements of Groups IIIB—VIIB. Formulas in italics refer to compounds of known structure.

III	IV	V	VI	VII
	Na_4Si [49] *NaSi* [50] $NaSi_2$ [51] Na_xSi_{136} [52] $(x \leq 11)$ Na_8Si_{46} [52, 232]	*Na_3P* [4] Na_2P [5, 45] NaP [45] Na_2P_5 [45] NaP_7 [238]	*Na_2S* [3, 36] *Na_2S_2* [37, 38] Na_2S_3 [39] Na_2S_4 [39] Na_2S_5 [39]	*NaCl* [2]
Na_5Ga_8 [62] *$NaGa_4$* [55, 63]	*NaGe* [50]	*Na_3As* [4] NaAs [46] Na_3As_7 [46] $NaAs_5$ [46]	*Na_2Se* [3, 36] *Na_2Se_2* [37] Na_2Se_3 [36, 40] Na_2Se_4 [36, 40] Na_2Se_6 [36, 40]	*NaBr* [2]
"Na_2In" [33] *NaIn* [33, 64] Na_5In_8 [33]	$Na_{15}Sn_4$ [53] Na_3Sn [54] Na_2Sn [54] Na_4Sn_3 [54] NaSn [54] $NaSn_2$ [54] $NaSn_3$ [54] $NaSn_4$ [55, 56] $NaSn_6$ [54]	*Na_3Sb* [4] *NaSb* [47]	*Na_2Te* [3, 36, 41] Na_2Te_2 [36, 41, 42] Na_2Te_3 [36, 43, 44] Na_2Te_4 [36, 43, 44] $NaTe_3$ [41, 42]	*NaI* [2]
Na_6Tl [65] *Na_2Tl* [66] *NaTl* [67] $NaTl_2$ [65]	Na_5Pb [57] *$Na_{15}Pb_4$* [53, 58] *$Na_{13}Pb_5$* [59] Na_5Pb_2 [59] *Na_9Pb_4* [59] *NaPb* [60] "*$NaPb_3$*" [61]	*Na_3Bi* [4] *NaBi* [48]		

Table 3. Compounds of potassium with elements of Groups IIIB—VIIB. Formulas in italics refer to compounds of known structure.

III	IV	V	VI	VII
	KSi [77] *K_8Si_{46}* [78, 232] KSi_6 [56]	*K_3P* [69] K_3P_2 [5] *KP_{15}* [70]	*K_2S* [36, 68] *K_2S_2* [37] K_2S_3 [36, 68] K_2S_4 [36, 68] K_2S_5 [36, 68] K_2S_6 [36, 68]	*KCl* [2]
K_5Ga_8 [63, 86] KGa_4 [55, 63, 86]	*KGe* [56, 77] KGe_4 [56] *K_8Ge_{46}* [78, 232]	*K_3As* [4] K_5As_4 [71] KAs [71] KAs_2 [71]	*K_2Se* [36] *K_2Se_2* [36], cited in [37] K_2Se_3 [36] K_2Se_4 [36] K_2Se_5 [36]	*KBr* [2]
K_5In_8 [33] *KIn_4*[55]	K_2Sn [79] *KSn* [80] KSn_2 [79, 81] KSn_4 [55, 56] *K_8Sn_{46}* [78]	*K_3Sb* [4] K_5Sb_4 [72] *KSb* [73] KSb_2 [72]	*K_2Te* [36] K_2Te_2 [36] K_2Te_3 [36]	*KI* [2]
KTl [33] K_4Tl_5 [33] K_5Tl_8 [33]	K_2Pb [82, 83] *KPb* [80] K_2Pb_3 [84] *KPb_2* [85] K_4Pb_9 [43] KPb_4 [82, 85]	*K_3Bi* [4] K_3Bi_2 [76] K_5Bi_4 [76] *KBi_2* [74, 75]		

2. Choice of Material: Zintl Phases

According to *Pauling*, the polarity of a covalent bond can be estimated from the difference in electronegativity of the participating atoms. If this is accepted at least qualitatively in spite of many justified objections for the case of a metallic bond, then transitions between metallic bonding and ionic bonding may be expected in those intermetallic compounds whose components exhibit considerable differences in electronegativity. This applies in particular to compounds of the alkali and alkaline earth metals with the electronegative metals, metametals, and semimetals of Groups IIIB to VB and the transition metals having almost filled d shells. However, the latter type of compounds have so far been only poorly characterized with regard to their structure, thus precluding any generalizations. They will consequently not be discussed further

Table 4. Compounds of rubidium with elements of Groups IIIB—VIIB. Formulas in italics refer to compounds of known structure.

III	IV	V	VI	VII
	RbSi [77] $RbSi_6$ [56] $RbSi_8$ [94]	Rb_2P_5 [89]	*Rb_2S* [36, 87] Rb_2S_2 [36, 88] Rb_2S_3 [36, 88] Rb_2S_4 [36, 88] Rb_2S_5 [36, 88] Rb_2S_6 [36, 88]	*RbCl* [2]
Rb_5Ga_8 [33] $RbGa_4$ [33]	*RbGe* [77] $RbGe_4$ [56]	*Rb_3As* [69]	Rb_2Se [36, 87] Rb_2Se_2 [36] Rb_2Se_3 [36] Rb_2Se_4 [36]	*RbBr* [2]
Rb_5In_8 [33] *$RbIn_4$* [55]	*RbSn* [80]	Rb_3Sb [69, 90—92] Rb_5Sb_2 [72], cf. also [92] Rb_5Sb_4 [72, 92] RbSb [72, 92] $RbSb_2$ [72, 92] Rb_3Sb_7 [72, 92]	Rb_2Te [36] Rb_2Te_2 [36] Rb_2Te_3 [36]	*RbI* [2]
Rb_4Tl_5 [33] $RbTl_2$ [33] $RbTl_3$ [33]	*RbPb* [80]	*Rb_3Bi* [69, 93] Rb_3Bi_2 [76] Rb_5Bi_4 [76] *$RbBi_2$* [69]		

Table 5. Compounds of cesium with elements of Groups IIIB—VIIB. Formulas in italics refer to compounds of known structure.

III	IV	V	VI	VII
	CsSi [77] $CsSi_8$ [94]		Cs_2S [36] Cs_2S_2 [36, 88] Cs_2S_3 [36, 88] Cs_2S_4 [36, 88] Cs_2S_5 [36, 88] *Cs_2S_6* [36, 88, 240]	*CsCl* [2]
Cs_5Ga_8 [33] $CsGa_4$ [33]	*CsGe* [77] $CsGe_4$ [56]	Cs_3As [69]	Cs_2Se [36]	*CsBr* [2]
Cs_5In_8 [33] $CsIn_4$ [33]	*CsSn* [80]	*Cs_3Sb* [69, 95] Cs_5Sb_2 [69] Cs_2Sb [72, 96] Cs_3Sb_2 [69, 96] Cs_5Sb_4 [69] CsSb [72, 96] Cs_3Sb_7 [69]	Cs_2Te [36]	*CsI* [2]
Cs_5Tl_7 [33] Cs_4Tl_7 [33] $CsTl_3$ [33]	*CsPb* [80]	*Cs_3Bi* [69, 97] Cs_3Bi_2 [76, 98] Cs_5Bi_4 [76] *$CsBi_2$* [76]		

in this report. The phases known to be formed by alkali and alkaline earth metals with the other B-group elements are listed in Tables 1 to 9. High-pressure, high-temperature, and ternary phases have been omitted, as have compounds of the less electropositive element beryllium and the hitherto hardly studied compounds of radium.

The compounds of alkali and alkaline earth metals with elements of Groups VIIB and VIB are usually typical salts with regard to their physical and chemical properties and their structures. The compounds with elements of Group VB progressively discard the characteristics of ionic bonding with increasing atomic number of the electronegative component. They become increasingly metallic in appearance and occur in stoichiometries that are not readily reconciled with valence rules for salts. This tendency is even more pronounced in compounds with Group IVB and IIIB elements and transition elements.

The transition between ionic bonding and metallic bonding in this class of compounds was first studied systematically by *Eduard Zintl* who prepared numerous intermetallic compounds listed in Tables 1—9 for the first time and investigated their structures. In recognition of his contribution to their study, *Zintl*'s obituary by *Laves*[11] listed all intermetallic compounds of Tables 1—9 obeying rules of valence—according to the views of the day—under the heading "Zintl phases".

In so doing he particularly emphasized two criteria:

"a) Zintl phases crystallize in "non-metallic" typically salt-like structures (antifluorite, anti-Mn_2O_3, anti-La_2O_3, antitysonite, anti-BiF_3 lattices).

Table 6. Compounds of magnesium with elements of Groups IIIB—VIIB. Formulas in italics refer to compounds of known structure.

III	IV	V	VI	VII
$Mg_{17}Al_{12}$ [117] $Mg_{23}Al_{30}$ [118, 119] Mg_2Al_3 [116], cf. [120, 121]	*Mg_2Si* [111—113]	*Mg_3P_2* [106, 107]	*MgS* [102]	*$MgCl_2$* [99]
Mg_5Ga_2 [122, 123] *Mg_2Ga* [123—125] *MgGa* [122, 123] *$MgGa_2$* [123, 126] *Mg_2Ga_5* [127]	*Mg_2Ge* [113—115]	*Mg_3As_2* [106—108] $MgAs_4$ [109]	*MgSe* [103]	*$MgBr_2$* [100]
Mg_3In [122, 128] *Mg_5In_2* [122, 129] *Mg_2In* [122] *MgIn* [129] *$MgIn_{2.5}$* [122, 129] *$\sim MgIn_5$* [122, 130]	*Mg_2Sn* [113—115]	*Mg_3Sb_2* [106, 110]	*MgTe* [104] *$MgTe_2$* [105]	*MgI_2* [101]
Mg_5Tl_2 [129] *Mg_2Tl* [124] *MgTl* [131]	*Mg_2Pb* [113—115]	*Mg_3Bi_2* [106]		

b) Zintl phases are always those phases of the alloy system concerned which contain the greatest amount of non-noble components."

The concept of Zintl phases was thus closely defined and coupled particularly *via* criterion b) with the condition that the upper limit of the alkali or alkaline earth metal in such compounds is determined by the maximum negative valence of the more electronegative element. However, this has proved to be inapplicable. Nor was any account taken of all those phases in which the anions are mutually linked by way of directional bonds as were frequently found in the ensuing period.

The difficulties arising from *Laves'* original definition of Zintl phases have led to repeated attempts at redefining the concept. It is usually approached crystallographically by metallurgists and crystallographers, who designate only cubic phases crystallizing in the NaTl lattice as Zintl phases. This covers only a very small group of compounds. In the language of the chemist, however, the term nowadays embraces intermetallic phases to which a pronounced ionic bonding component must be assigned. This limitation, while in accord with the aims of *Zintl's* work, has the disadvantage of being imprecise. Thus ionic bonding contributions were also discussed for Hume-Rothery[210] and for Laves

Table 7. Compounds of calcium with elements of Groups IIIB—VIIB. Formulas in italics refer to compounds of known structure.

III	IV	V	VI	VII
$CaAl_2$ [154] *$CaAl_4$* [155]	Ca_7Si [140] *Ca_2Si* [141] *Ca_5Si_3* [142] *CaSi* [143] *$CaSi_2$* [144, 145]	Ca_3P_2 [134] CaP [134] CaP_5 [135, 136]	*CaS* [102]	*$CaCl_2$* [132]
Ca_3Ga [156] Ca_5Ga_2 [156] Ca_2Ga [156] *CaGa* [156] *$CaGa_2$* [157] *$CaGa_4$* [158]	$Ca_{33}Ge$ [146] *Ca_7Ge* [146] *Ca_2Ge* [141] *CaGe* [147, 148] *$CaGe_2$* [150]	Ca_3As_2 [109, 137] $CaAs_4$ [109]	*CaSe* [133]	*$CaBr_2$* [132]
Ca_3In [159] *CaIn* [159] *$CaIn_2$* [160]	*Ca_3Sn* [209] *Ca_2Sn* [149] *CaSn* [148] *$CaSn_3$* [151]	Ca_7Sb_4 [138]	*CaTe* [133]	*CaI_2* [132]
Ca_3Tl [161] Ca_5Tl_2 [161] Ca_3Tl_2 [161] *CaTl* [162] Ca_3Tl_4 [163] *$CaTl_3$* [153]	*Ca_3Pb* [146] *Ca_2Pb* [149] *Ca_5Pb_3* [146] CaPb [152] *$CaPb_3$* [153]	Ca_7Bi_4 [138] $CaBi_3$ [139]		

Table 8. Compounds of strontium with elements of Groups IIIB—VIIB. Formulas in italics refer to compounds of known structure.

III	IV	V	VI	VII
SrAl [184] *$SrAl_2$* [185] *$SrAl_4$* [184]	Sr_7Si [140] *Sr_5Si_3* [172] *SrSi* [173, 208] *Sr_4Si_7* [174] *$SrSi_2$* [175]	Sr_2P [166] *Sr_3P_2* [166] Sr_4P_3 [166] SrP [166] *Sr_3P_{14}* [239]	*SrS* [102] SrS_2 [164] SrS_3 [164]	*$SrCl_2$* [132]
Sr_3Ga_2 [156] *$SrGa_2$* [186] *$SrGa_4$* [158]	Sr_2Ge [176] *SrGe* [177—179] *Sr_3Ge_4* [229] *$SrGe_2$* [180]	Sr_3As_2 [167]	*SrSe* [102]	*$SrBr_2$* [132]
Sr_3In [187] Sr_3In_2 [187] SrIn [187] Sr_2In_3 [187] *$SrIn_2$* [160] Sr_2In_5 [187] $SrIn_3$ [187] $SrIn_5$ [187]	"Sr_2Sn" [181] *SrSn* [179] $SrSn_3$ [182] $SrSn_5$ [182]	Sr_2Sb [138] Sr_3Sb_2 [168] SrSb [168] $SrSb_3$ [168]	*SrTe* [165]	*SrI_2* [132]
Sr_3Tl [161] SrTl [161] *SrTl* [34, 161] *$SrTl_2$* [160, 161] *$SrTl_3$* [161]	"Sr_2Pb" [181] SrPb [183] *$SrPb_3$* [153]	Sr_2Bi [138] Sr_3Bi_2 [169, 170] SrBi [169, 170] *$SrBi_3$* [171]		

Table 9. Compounds of barium with elements of Groups IIIB—VIIB. Formulas in italics refer to compounds of known structure.

III	IV	V	VI	VII
Ba_9Al [204] Ba_9Al_2 [204] BaAl [205] $BaAl_2$ [160] *$BaAl_4$* [206]	*Ba_5Si_3* [196] *BaSi* [197, 198] *Ba_3Si_4* [200] *$BaSi_2$* [199]	"Ba_2P" [191] *Ba_3P_2* [191, 192] Ba_4P_3 [191] $Ba_{1.1}P$ [191] Ba_4P_5 [191] $BaP_{1.82}$ [191] BaP_2 [191] *BaP_3* [191, 237]	Ba_2S [190] *BaS* [188] BaS_2 [189] *BaS_3* [189]	*$BaCl_2$* [132]
Ba_3Ga_2 [156] BaGa [156] *$BaGa_2$* [186] *$BaGa_4$* [158]	*Ba_2Ge* [201] *BaGe* [179, 197] *$BaGe_2$* [180]	Ba_3As_2 [193]	*BaSe* [165]	*$BaBr_2$* [132]
$Ba_{13}In$ [187] Ba_3In [187] Ba_2In [187] BaIn [187] *$BaIn_2$* [187, 207] *$BaIn_4$* [158]	*BaSn* [179] $BaSn_3$ [202] $BaSn_5$ [202]	Ba_3Sb_2 [194]	*BaTe* [165]	*BaI_2* [132]
$Ba_{13}Tl$ [161] Ba_2Tl [161] BaTl [161] *$BaTl_2$* [160, 161] $BaTl_3$ [161] $BaTl_4$ [161]	Ba_2Pb [194] *Ba_5Pb_3* [203] *BaPb* [203] *$BaPb_3$* [203]	$Ba_{2.2—2.4}Bi$ [138] Ba_3Bi_2 [195] BaBi [195] *$BaBi_3$* [171]		

phases[211]. A new definition of the term "Zintl phases" therefore appears desirable and a relevant proposal will be presented at the close of this survey.

3. Preparation

The intermetallic compounds to be considered are generally obtained by fusing the elements together under an inert gas or in air under a protective salt melt. Subsequent purification is possible only in favorable cases (zone refining). When an unknown system is examined for new phases the method usually yields mixtures of compounds. The ratio of components must then be varied while a phase diagram is recorded until a homogeneous product is obtained. With metastable and peritectic compounds the conditions of preparation represent additional experimental parameters.

This time-consuming and tedious work is simplified by the particularly favorable circumstance that all metals and intermetallic compounds are deposited in crystalline form

from the melt. Carefully conducted cooling and annealing procedures often permit isolation of the phases formed from the melt as coarse crystals so that single crystals can be broken out of the reguli and their composition determined by modern microanalytical methods.

Methods of preparing intermetallic phases other than direct synthesis from the elements are usually limited in their application to particular systems and therefore of comparatively limited importance. Mention should be made of:

1. Direct reduction of generally oxidic compounds by carbon or hydrogen to the corresponding intermetallic compounds, *e.g.*:

$$2\,CaCO_3 + 4\,SiO_2 + 5\,C \rightarrow 2\,CaSi_2 + 7\,CO_2 \quad [144]$$

$$CaO + 2\,Pt + H_2 \rightarrow CaPt_2 + H_2O \quad [212]$$

2. Preparation in liquid ammonia. This technique is due mainly to *Zintl* who exploited the known solubility of alkali and alkaline earth metals in liquid NH_3 for the synthesis of compounds of these elements with other metals. For instance, a solution of Na in NH_3 is able to dissolve Pb metal, the reaction being considerably promoted by fine division of the reactant. For experimental purposes, therefore, a dissolved salt of the electronegative metal, *e.g.* PbI_2, ZnI_2, $Hg(CN)_2$, or even As_2S_3, in liquid NH_3 is reduced with a similar solution of Na. The resulting finely divided metal reacts in the same solvent to give the intermetallic compounds[43,114].

3. Amalgam metallurgy. This technique utilizes the solubility of numerous metals in mercury to prepare intermetallic compounds, the mercury being distilled off after reaction of the dissolved metals[213–215]. The method was developed only recently and has not yet been exploited to its limits of applicability. It is comparable with the method of preparing intermetallic compounds in a copper or aluminum matrix as already used by *Lebeau et al.*[216] and *Hönigschmid*[217].

Mainly physical methods are used in recording phase diagrams and testing for homogeneity: microscopic investigations, thermal analysis, determination of thermal conductivity, magnetic measurements, X-ray techniques, and recently in particular investigations with microprobes. In addition to classical analysis, X-ray structure determinations frequently prove of value in establishing the stoichiometry of an unknown phase. It is only with their help that exact stoichiometric studies could be performed for numerous compounds of highly complicated composition.

4. Characterization of the Bonding State

4.1. Physicochemical Criteria

The known characteristic properties of salts are employed in characterizing ionic bonding contributions. Such a property is the solubility in polar solvents. The phases discussed here cannot be dissolved without decomposition. However, in his studies in liquid NH_3 *Zintl* was able to show that in addition to halogens and chalcogens the elements of Groups VB and IVB are in principle able to form anions too. If *e.g.* Na is allowed to react with PbI_2 in liquid NH_3 as described in Section 3, and an excess of Pb salt is employed then deeply colored solutions are obtained. Measurement of transport numbers in these solutions indicate the presence of polyanions, *e.g.* Pb_9^{4-}, thus revealing the polar character of such compounds[43,114]. However, they are only stable as ammonia adducts; on evaporation of the solvent they decompose with destruction of the polyanions. Those elements shown by such experimental findings to be capable of occurring in a negatively charged state in solution are bounded by the so-called Zintl line in the Periodic Table. This line of demarcation runs between Groups IIIB and IVB. Recently, *Kummer et al.*[218] showed that analogous reactions also occur in aliphatic diamines. It proves particularly fortunate that crystalline compounds, *e.g.* $Na_4Sn_9 \cdot 6$ en, could be obtained in this way which will probably allow the structure of "Zintl polyanions" to be elucidated by X-ray methods in the near future.

The heat of formation of these compounds can also be employed in characterizing their bonding. Whereas alloy formation between metals of low electronegativity difference involves only a low heat tone, the heats of formation of Zintl phases are in some cases comparable with those of salt-like compounds. They can therefore be regarded as an indication of polar bonding contributions. Available experimental evidence is still too fragmentary for a systematic evaluation.

A similar lack of completeness attends the existing data on characteristic physical properties arising from the bonding in compounds of such systems. Their electrical conductivity and magnetism are known only in rare cases and provide no basis for systematization.

In contrast, the density has be measured for many of the compounds listed in Tables 1—9. *Biltz* had reported that the formation of heteropolar compounds from the elements is associated with a particularly pronounced volume contraction. Such effects are also noted with intermetallic compounds between components of widely differing electronegativity. In a systematic evaluation of the data then available *Biltz et al.* showed that in intermetallic compounds the alkali and alkaline earth metals undergo a volume contraction to a limited value of the volume ("increment") which is largely independent of the composition of the alloy[219]. These values were subsequently confirmed, in some cases several times, in other systems[72,212,236]. Table 10 lists the increments, the atomic volumes, and the percentage contractions. The values clearly demonstrate that the reduction in volume on formation of alkali and alkaline earth metal compounds with elements of Groups IB and IIB substantially involves the non-noble component while the noble metals undergo only relatively slight contraction if any. This accords with the observation of interatomic distances in compounds having alkali metal-alkali metal or alkaline earth metal-alkaline earth metal neighbors that are sometimes even considerably smaller than those in the elements. In terms of ionic bonding this preferential contraction of the alkali and alkaline earth metal could be attributed to loss of electrons and thus to the transition to the smaller cation. Another feature

Table 10. Comparison of atomic volumes with the increments in intermetallic phases of the alkali and alkaline earth metals with B-group elements (values taken from *Biltz* [212]).

Element	Atomic volume	Increment	% Contraction	Element	Atomic volume	Increment	% Contraction
Li	12.6	8 to 9	36.5 to 28.6	B	3.25	3.4	−4.6
Na	22.8	17	25.4	Al	9.9	10	−1.0
K	43.4	25	42.4	Ga	11.7	8 to 9	31.6 to 23.1
Rb	53.1	29	45.4	In	15.3	13.4	12.4
Cs	65.9	33	49.9	Tl	16.9	15.2	10.1
Cu	7.05	6.6	6.4	C	$3.41_{diamond}$ / $5.38_{graphite}$	3.3	3.2 / 38.7
Ag	10.13	10	1.3	Si	12.03	7	41.8
Au	10.12	10	1.2	Ge	13.5	9	33.3
Be	4.84	4.6	5.0	Sn	16.0	14 to 20	+12.5 to −25.0
Mg	13.8	13	5.8		20.5		31.7 to 2.4
Ca	25.6	18.5	27.7	Pb	17.9	17	5.0
Sr	33.2	23.5	29.2				
Ba	37	29.5	20.3				
Zn	8.9	8.8	1.1	P	11.4_{black} / 13.2_{red} / 15.4_{white}	10	12.3 / 24.3 / 35.1
Cd	12.7	12.6	0.8	As	13.0	11	15.4
Hg	13.75	13.4	2.5	Sb	18.1	14	22.7
				Bi	21.0	?	-

of Table 10 is that the elements of Groups IIIB and IVB also suffer contractions on compound formation which in some cases, *e.g.* Ge, Si, is hardly less pronounced than for the alkali or alkaline earth metals. On the other hand, crystal structure determinations which are readily available in particular for systems of the two elements given indicate that larger atomic distances than in the element are by far more common in compounds having Ge—Ge or Si—Si bonds. These two findings would appear contradictory at first glance. It should, however, be borne in mind that considerable covalent bonding is already present in the lattices of the semi- and meta-metals which results in atomic arrangements that are very bulky owing to directional bonding. On compound formation these voluminous lattices are broken open and considerably denser atomic packings become possible although the bond lengths are greater.

4.2. Spectroscopic Studies

Spectroscopic methods should, at least in principle, permit measurement of charge shifts between the components corresponding to ionic bonding contributions. The method of choice is X-ray spectroscopy, which has already provided valuable information for other classes of compounds[220].

When an atom enters into chemical bonding the energy of the inner shells is also modified. For instance, if the atom acquires a positive charge on compound formation the inner electrons become more firmly bound while acquisition of a negative charge leads to the opposite effect. The electrons occupying different levels all change their energy in the same sense but not by the same amount. If the characteristic X-ray spectrum of the atom is recorded on a high-resolution spectrograph the spectral lines are found to be shifted slightly relative to those recorded for the elemental state: they display a chemical shift. The shifts of the Kα line of Third Row elements are particularly readily measurable and have been the object of recent detailed studies. Accordingly, the Kα line of an element shows an increasingly pronounced short-wave shift with increasing oxidation number and increasing electronegativity of its bonding partner. However, it has also become apparent that additional factors, such as changes in coordination number, the shape of the coordination polyhedron (hybridization), and even the bond lengths *etc.*, are also operative in determining the chemical shift so that the position of the Kα line recorded for the element in question cannot be taken as the reference point for zero charge[221, 222]. Owing to these additional parameters an estimation of heteropolar bonding components by Kα spectroscopy will have to wait until completion of a broad-based study of the class of compounds under consideration supplemented by theoretical calculations. The material available is still rather meager. Measurements have been performed, *inter alia*, on Li_4Si, Mg_2Si, and Ca_2Si[223], and $CaSi_2$[224] (Si-Kα line in all cases), as well as $CaAl_2$[225] (Al-Kα). Without exception the shifts relative to the elemental state are very small or lie within the limits of accuracy of the method.

Similar difficulties are encountered in X-ray photoelectron spectroscopy (ESCA). On irradiation of an atom with sufficiently short wave X-ray quanta, electrons from the inner shells can depart from the atomic system with absorption of an X-ray quantum. Measuring the kinetic energy of the leaving photoelectrons yields information about the binding energy of these electrons prior to the absorption. Whereas X-ray spectroscopy always yields the difference in energy between two electronic levels, X-ray photoelectron spectroscopy provides a direct indication of the binding energy of the core electrons. Changes in binding energies relative to the elemental state, which are also designated chemical shifts, can thus be determined. According to *Siegbahn et al.*[234] these changes can be described by a simple ionic model, the chemical shift being proportional to the effective charge of the atom studied. A positive charge leads to a higher binding energy and a negative charge to a lower binding energy. Recent work on solids has shown, however, that additional parameters have to be considered as in the chemical shift of the Kα line.

Only few measurements on alkaline earth metal silicides have so far be carried out[226] from which, with all due reservations, a negative charge on the silicon is indicated by the simple ionic model.

4.3. Structural Studies

The results of X-ray crystal structure determinations have assumed great significance in discussions of the bonding in these phases. Relatively speaking, this is the field with the greatest amount of experimental material and will therefore now be considered in detail.

According to the structural findings, the class of compounds under study can be divided up into several large groups.

4.3.1. Phases Obeying the Zintl-Klemm-Busmann Concept

Zintl himself showed in numerous preparative and structural studies that alkali and alkaline earth metals could undergo combination *inter alia* with Group VB elements to give products having compositions stoichiometrically analogous to those expected for salts with element(V) anions (A^{3-} ions) having complete octets: M^{I}_3A or $M^{II}_3A_2$. A corresponding situation prevails with Group IVB elements only for some compounds with alkaline earth metals (Tables 11, 12, and 13). A common feature of all lattice types encountered here is that they lead to "isolated" element(V) or element(IV) atoms. The expression "isolated atoms" means that they have only other kinds of atoms as nearest neighbors, *i.e.* the distance to another atom of the same kind in the lattice is so great that no direct interaction can be assumed between them. The conditions for maximally uniform charge distribution throughout the lattice are thereby fulfilled and such lattice types are indeed found particularly frequently in the typical salts. *Zintl* consequently regarded this as an indication of a heteropolar bonding component in such phases.

Table 11. Lattices of alkali metal compounds with Group VB elements of stoichiometry A_3X.

	P	As	Sb	Bi
Li	Na_3As	Na_3As	Na_3As, Li_3Bi	Li_3Bi
Na	Na_3As	Na_3As	Na_3As	Na_3As
K	Na_3As	Na_3As	Na_3As	Na_3As
Rb	—	Na_3As	Na_3As	Li_3Bi
Cs	—	?	Li_3Bi	Li_3Bi

—: compound unknown; ?: structure unknown.
Na_3As, Li_3Bi ≙ structural type designation.

Table 12. Lattices of alkaline earth metal compounds with Group VB elements of stoichiometry A_3X_2.

	P	As	Sb	Bi
Be	—	—	—	—
Mg	anti-Mn_2O_3	anti-Mn_2O_3	anti-La_2O_3	anti-La_2O_3
Ca	?	?	—	—
Sr	anti-Ce_2S_3	?	?	?
Ba	anti-Ce_2S_3	?	?	?

—: compound unknown; ?: structure unknown.
anti-Mn_2O_3, anti-La_2O_3, anti-Ce_2S_3 ≙ structural type designation.

Table 13. Lattices of alkaline earth metal compounds with Group IVB elements of stoichiometry A_2X.

	Si	Ge	Sn	Pb
Be	—	—	—	—
Mg	anti-CaF_2	anti-CaF_2	anti-CaF_2	anti-CaF_2
Ca	anti-$PbCl_2$	anti-$PbCl_2$	anti-$PbCl_2$	anti-$PbCl_2$
Sr	—	—	—	—
Ba	—	anti-$PbCl_2$	—	—

—: compound unknown.
anti-CaF_2, anti-$PbCl_2$ ≙ structural type designation.

In addition to the compounds exhibiting stoichiometries similar to those of the salts, systems of alkali and alkaline earth metals with Group VB, IVB, and IIIB elements contain many compounds not having this kind of composition. Structurally it is found that in these phases partial element(V), element(IV), or element(III) lattices are formed for which direct bonding between element(V), element(IV), or element(III) atoms has to be assumed from the observed interatomic distances. In order to explain these partial lattices a concept was developed that is based essentially on *Zintl*'s interpretation of the LiAl and NaTl lattices (Fig. 1). Concerning the structure of these compounds Zintl wrote: "There results... the concept of a skeleton made up of atoms B (B = element of Group IIIB) and supporting the crystal structure whose vacant sites are filled with Li or Na particles. The skeleton of B atoms is a diamond lattice such as exists *per se* only with C, Si, Ge, or Sn atoms, which are all characterized by having four valence electrons. The atoms of Al, Ga, In, Tl all have one electron too few to be able to form a diamond lattice. This deficit can, however, be compensated by incorporation of one atom of Li or Na (one valence electron per atom) per atom of Al, Ga, In, or Tl; there thus arises a diamond lattice of the last mentioned atoms whose vacancies contain the cores of the alkali atoms furnishing the electrons. That the spatial requirements of the alkali atoms under such conditions are considerably smaller than in the free metal likewise becomes understandable, for their

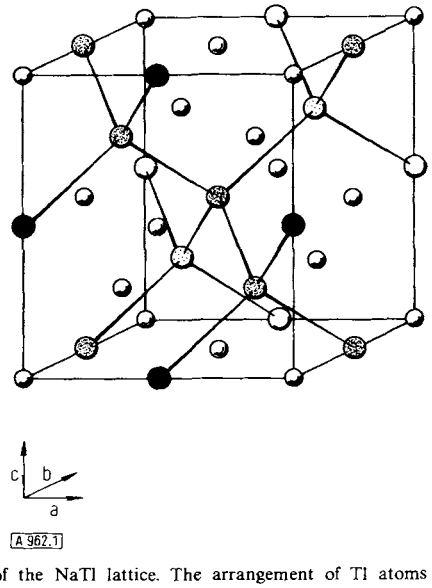

Fig. 1. Unit cell of the NaTl lattice. The arrangement of Tl atoms is emphasized (after ref. [227]).

internal function in the crystal structure lies in the direction of the transition to the much smaller alkali ion."

On the basis of available experimental evidence, which has meanwhile considerably increased, *Klemm* and *Busmann* have generalized this interpretation of the NaTl lattice[228]. Formulated in extreme terms, the non-noble metal transfers electrons to the more noble component of the alloy, the "anion former". With the resulting outer electronic configuration an "anion partial lattice" is constructed whose atomic arrangement corresponds to the element having the same number of valence electrons (Zintl-Klemm-Busmann concept).

The compounds obeying the Zintl-Klemm-Busmann concept are listed in Table 14 and compounds with particularly characteristic anionic partial lattices are represented in Figures 1 to 9. They impressively demonstrate the analogy to the corresponding elemental lattices.

However, Table 14 also contains compounds whose anion lattices are not isosteric with elemental lattices having the same number of valence electrons. Thus the alkaline earth metal compounds crystallizing in the CrB type form planar zig-zag chains of element(IV) atoms whereas the chains occurring in the Group VIB elemental structures are helical. The two-coordination of the atoms is however retained. $SrSi_2$[175] and LiGe[22] contain a three-dimensional Si or Ge structure (Figs. 6 and 7) which has not yet been observed in the elements of Group VB (Si^- and Ge^- being isoelectronic with the Group VB elements with regard to the number of valence electrons). In the anion partial lattices found, each atom has three other atoms of the same kind as nearest neighbors. The four atoms construct a flat distorted trigonal bipyramid whose base atoms each represent the apices of adjoining pyramids. The basal faces of these pyramids are mutually twisted, giving rise to a three-dimensional network. In contrast,

Table 14. Compounds obeying the Zintl-Klemm-Busmann concept. The coordination in the anion partial lattices conforms to the $(8-N)$ rule.

N	Cpd.	Formal charge	Coordination	Structure of anion partial lattice	Structural type	Bond lengths in anion partial lattice [Å]
4	LiAl	1−	4	three-dimensional network	NaTl	2.76
	LiGa			of tetrahedrally coordinated	NaTl	2.68
	LiIn			X atoms (≙ diamond)	NaTl	2.94
	NaIn				NaTl	3.16
	NaTl				NaTl	3.24
	$CaIn_2$	1−	4	three-dimensional network	$CaIn_2$	2.91–3.18
	$SrIn_2$			of distorted tetrahedrally	$CaIn_2$	2.98–3.27
	$SrTl_2$			coordinated X atoms	$CaIn_2$	3.03–3.32
	$BaTl_2$				$CaIn_2$	3.10–3.48
	$SrAl_2$				KHg_2	2.79–2.80
5	NaSi	1−	3	isolated X_4 tetrahedrons	NaSi	2.39–2.51
	NaGe			(≙ P_4)	NaGe	2.53–2.58
	NaPb				NaPb	3.15–3.16
	KSi				KGe	2.43
	KGe				KGe	2.56
	KSn				NaPb	2.98
	KPb				NaPb	
	RbSi				KGe	2.46
	RbGe				KGe	2.58
	RbSn				NaPb	
	RbPb				NaPb	
	CsSi				KGe	2.44–2.46
	CsGe				KGe	2.59–2.62
	CsSn				NaPb	
	CsPb				NaPb	
	$SrGe_2$	1−	3	isolated X_4 tetrahedrons	$BaSi_2$	2.50–2.58
	$BaSi_2$			(≙ P_4)	$BaSi_2$	2.34–2.48
	$BaGe_2$				$BaSi_2$	
	$CaSi_2$	1−	3	layers of infinite puckered hexagonal networks (≙ As)	$CaSi_2$	2.41
	$SrSi_2$	1−	3	three-dimensional network	$SrSi_2$	2.41
	LiGe	1−	3	of three-coordinate Si atoms	LiGe	2.55–2.60
6	CaSi	2−	2	planar zig-zag chains	CrB	2.46
	CaGe				CrB	2.60
	CaSn				CrB	2.91
	SrSi				CrB	2.51
	SrGe				CrB	2.62
	SrSn				CrB	2.92
	BaSi				CrB	2.51
	BaGe				CrB	2.63
	BaSn				CrB	2.97
	BaPb				CrB	3.13
	LiP	1−	2	screwed chains	LiAs	
	LiAs			(= Se, Te)	LiAs	2.45–2.47
	NaSb				LiAs	2.85–2.86
	KSb				LiAs	2.81–2.88

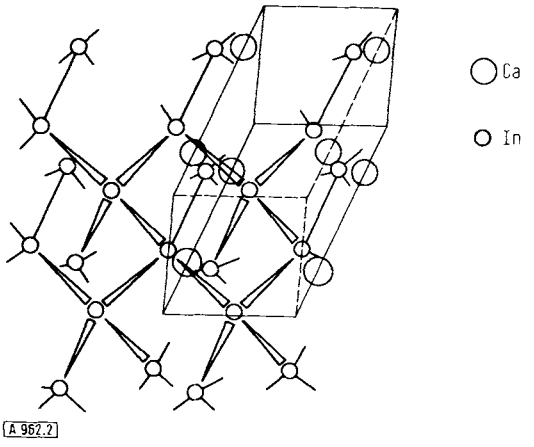

Fig. 2. Atomic arrangement in $CaIn_2$. The In partial lattice is emphasized.

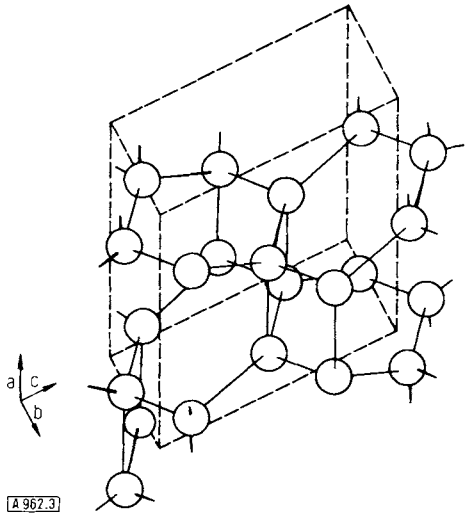

Fig. 3. Arrangement of Al atoms in $SrAl_2$.

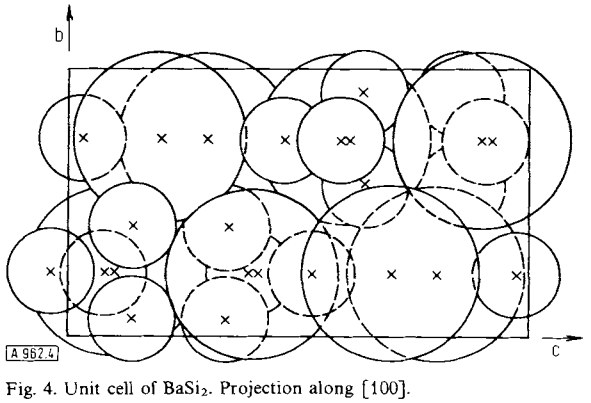

Fig. 4. Unit cell of $BaSi_2$. Projection along [100].

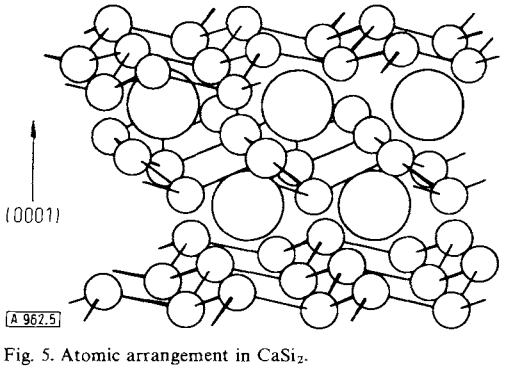

Fig. 5. Atomic arrangement in $CaSi_2$.

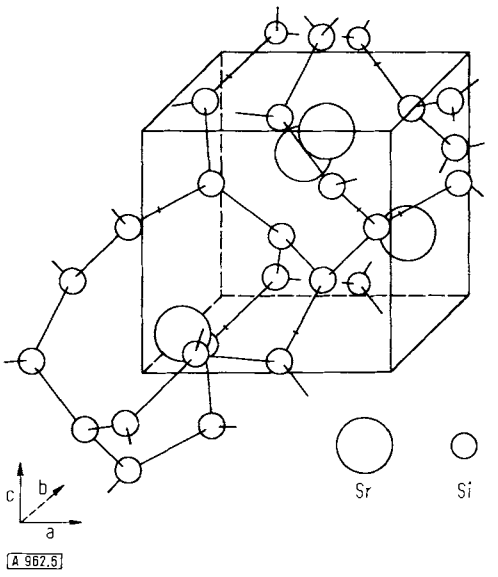

Fig. 6. Unit cell of $SrSi_2$.

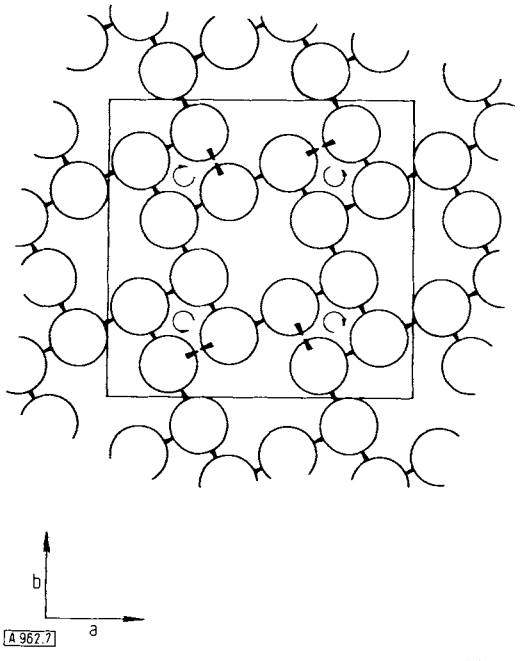

Fig. 7. Schematic arrangement of the Ge atoms in LiGe. Fourfold Ge screws are crosslinked with one another to give a three-dimensional skeleton.

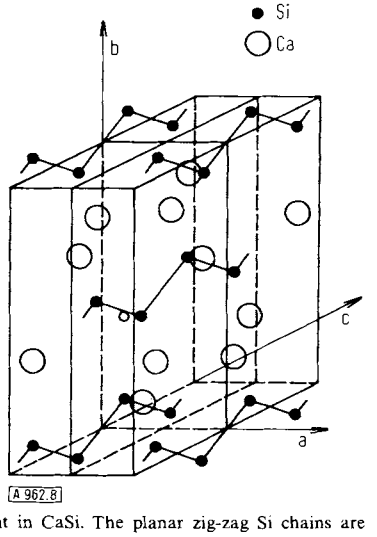

Fig. 8. Atomic arrangement in CaSi. The planar zig-zag Si chains are emphasized.

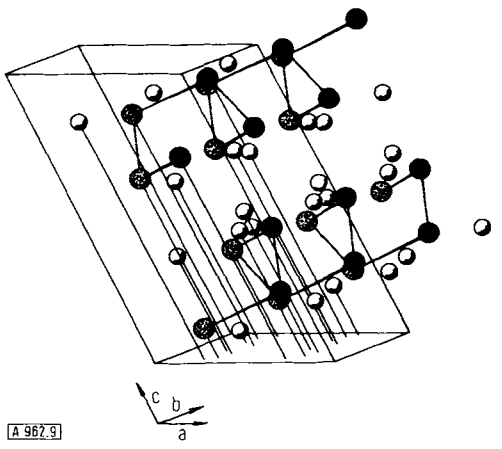

Fig. 9. Atomic arrangement in LiAs. The screwed As chains are emphasized (after ref. [227]).

the Si pyramids in $CaSi_2$ are arranged in parallel planes (Fig. 5) resulting in a Si layer structure corresponding to metallic As.

These findings suggest that the limitation of the concept to the lattices of the elements may reasonably be dropped in favor of an extension of its validity to ensure the same number of bonds to neighbors of the same species, *i.e.* the $(8-N)$ rule should be fulfilled. The general valence rule of *Pearson*[227] also leads to the same result. According to this rule, phases made up of elements on opposite sides of the Zintl line comply to the condition:

$$\frac{n_e + b_a - b_c}{n_a} = 8$$

(n_e = total number of valence electrons; n_a = number of anions; b_a = number of electrons required for formation of anion-anion bonds; b_c = number of electrons required for formation of cation-cation bonds, including all valence electrons of the cations not participating in a bond.) There results, *e.g.* for $CaSi_2$ ($n_e = 10$; $n_a = 2$; $b_c = 0$), a value of $b_a = 6$ bonding electrons, *i.e.* a coordination number of 3 for the anion partial lattice.

Apart from compounds whose anionic atoms are assigned integral formal charges in an ionic formulation there are others which in a corresponding formulation have fractional charges but whose anion partial lattices nevertheless are closely related to those of the former compounds (Table 15).

Ionic formulation of Li_7Si_2 and Li_7Ge_2[12,17] leads to a formal charge of 3.5− on the element(IV) atoms. Figures 10 and 11 each show two sections through the unit cell that alternate in the cells. In both structures there are four isolated element(IV) atoms and two Si_2 or Ge_2 dumbbells per unit cell. According to these structural principles the formulas can be broken down in the following way:

$$2\,Li_7Si_2 \rightarrow \text{“}2\,Li_4Si\text{”} + \text{“}Li_6Si_2\text{”}$$
$$2\,Li_7Ge_2 \rightarrow \text{“}2\,Li_4Ge\text{”} + \text{“}Li_6Ge_2\text{”}$$

Formally, not only Si^{4-} ions but also Si_2^{6-} ions have to be considered, the latter being isoelectronic to Cl_2 dumbbells.

Ca_5Si_3[142], Sr_5Si_3[172], Ba_5Si_3[196], and Ba_5Pb_3[203] require a formal charge of 3.33− on the element(IV) atoms. While not being isotypic, these compounds have largely analogous structures. As an example, Fig. 12 shows a section of the structure of Ca_5Si_3. The unit cell contains four Si_2 dumbbells and four isolated Si atoms so that these formulas can also be broken down in line with the same principle, *e.g.*

$$Ca_5Si_3 \rightarrow \text{“}Ca_2Si\text{”} + \text{“}Ca_3Si_2\text{”}$$

For Ba_3Si_4[200], Sr_3G_4[229], and $Ca_{0.5}Sr_{2.5}Si_4$[142], ionic formulation leads to 1.5 negative charges on the element(IV)

Table 15. Compounds having a fractional formal charge on the element(IV) atom when formulated ionically.

Cpd.	Formal charge on X atom according to formula	Coordination	Structure of anion partial lattice	Bond lengths [Å] in anion partial lattice
Li_7Si_2	$Si^{3.5-}$	1 and 0	isolated X atoms and X_2 dumbbells (= Group VII B)	2.38
Ca_5Si_3				2.44
Sr_5Si_3	$X^{3.33-}$	1 and 0		2.50
Ba_5Si_3				2.70
Ba_5Pb_3				3.05
Ba_3Si_4	$Si^{1.5-}$	3 and 2	isolated Si_4 units of two- and three-coordinate Si atoms	2.29–2.34
$Ca_{0.5}Sr_{2.5}Si_2$	$X^{1.5-}$	3 and 2	one-dimensional planar ribbon of hexagons of two- and three-coordinate X atoms	2.39–2.52
Sr_3Ge_4				
SrSi (2nd mod.)	Si^-	3, 2 and 1	isolated Si_{10} unit of three-, two-, and one-coordinate Si atoms	2.39–2.58
Sr_4Si_7	$Si^{1.14-}$	3 and 2	three-dimensional network of three- and two-coordinate Si atoms	2.34–2.48

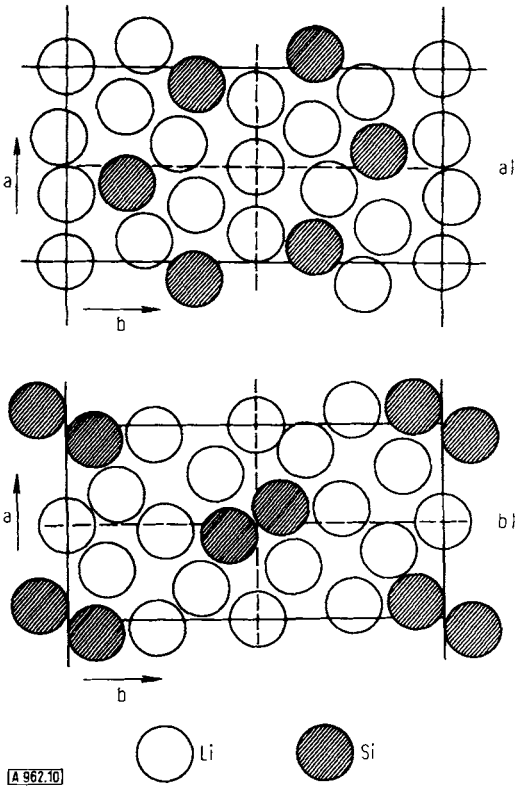

Fig. 10. Section through the unit cell of Li_7Si_2: a) $||a,b$ at $z = 0$; b) $||a,b$ at $z = 0.5$.

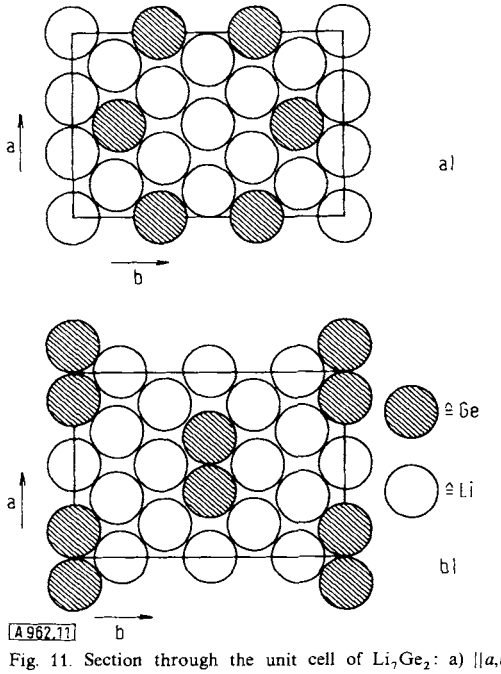

Fig. 11. Section through the unit cell of Li_7Ge_2: a) $||a,b$ at $z = 0$; b) $||a,b$ at $z = 0.5$.

atom. Figure 13 represents the isolated Si_4 unit occurring in the lattice of Ba_3Si_4. The Si atoms are arranged at the corners of two congruent isosceles triangles sharing the short base and oriented at an angle of 113° to each other. This Si unit can be derived from a Si_4 tetrahedron having one edge extended to such a degree that direct Si—Si interaction is no longer possible. However, differing coordinations of the Si atoms will occur: the Si atoms

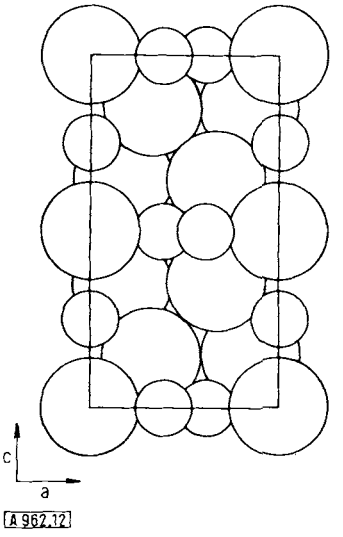

Fig. 12. Atomic arrangement in Ca_5Si_3. Projection of the unit cell onto the *a,c* plane.

on the common edge have three neighbors of the same species and those on the apices of the triangles two. To take account of this finding the three-coordinate Si atoms must be ascribed a negative charge because they correspond in their coordination to the elements of Group VB, while the two-coordinate ones are ascribed two charges because they resemble the dicoordinate Group VIB elements. Thus the overall Si_4 structural unit has six negative charges balanced by three Ba "ions".

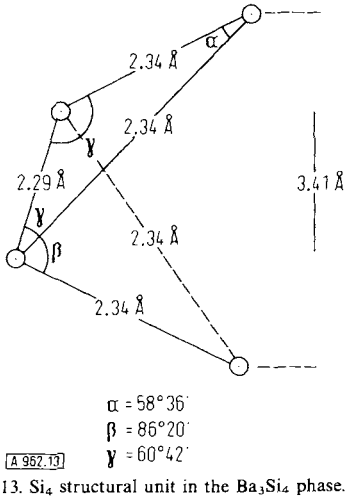

Fig. 13. Si_4 structural unit in the Ba_3Si_4 phase.

The atomic arrangement in the two isotypic phases Sr_3Ge_4 and $Ca_{0.5}Sr_{2.5}Si_4$ is depicted in Fig. 14. Planar Si or Ge hexagons are present which are coupled by way of opposite sides to form a one-dimensional infinite ribbon of hexagons. Although the structural principle is so very different from that of Ba_3Si_4, the same ratio of two- and three-coordinate Si atoms is observed in both cases, thus permitting assignment of a completely analogous charge distribution in accord with an ionic formulation.

These results show that for phases exhibiting fractional charges on the anionic components the charges may be resolved into the nearest integral values. The coordination

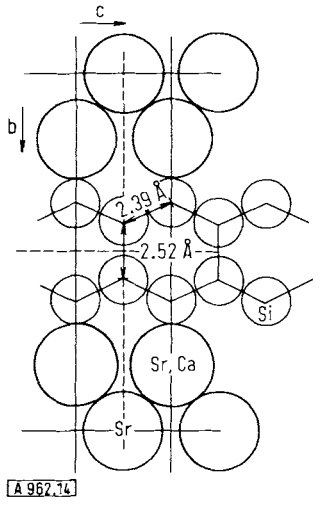

Fig. 14. Atomic arrangement in $Ca_{0.5}Sr_{2.5}Si_4$. Section at $x=0$.

in the anion partial lattice can accordingly be derived from the $(8-N)$ rule.

An analogous interpretation can also be given for the alkali metal and alkaline earth polyphosphides which have recently been elucidated by *von Schnering et al.* With the exception of Sr_3P_{14}, they all exhibit highly condensed, relatively complicated partial lattices of two- and three-coordinate phosphorus. It was found that in BaP_3[237] (with a mean formal charge of 0.666−) one three-coordinate (≙formal charge 0) and two two-coordinate phosphorus atoms (≙element of Group VIB ≙ formal charge 1−) per formula unit are balanced by one Ba^{2+} "ion". In completely analogous fashion, the P partial lattices of LiP_5 and LiP_7[238] each contain one two-coordinate P atom alongside four and six three-coordinate P atoms respectively. In KP_{15}[70] a two-coordinate P atom is accompanied by 14 three-coordinate P atoms which in this case

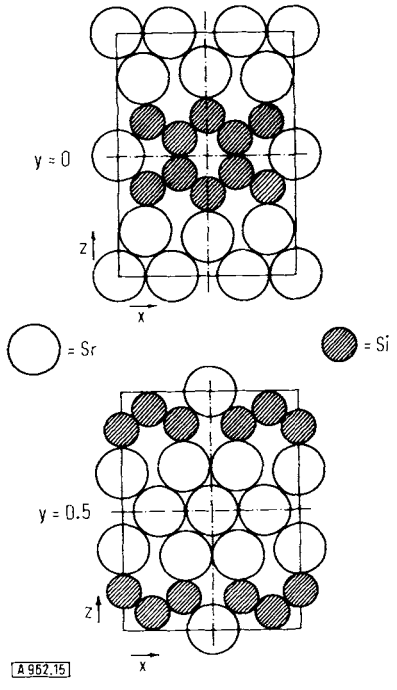

Fig. 15. Atomic arrangement of the second modification of SrSi.

are linked together to form structural units corresponding to those in Hittorf phosphorus[231]. A particularly clear example for the combination of two-coordinate and three-coordinate phosphorus atoms according to formal charge is also provided by the above-mentioned compound Sr_3P_{14}[239], in which isolated P_7^{3-} groups have been found. One P_7^{3-} unit contains four three-coordinate and three two-coordinate P atoms linked in complete analogy to the P_4S_3 molecule in which four three-coordinate P atoms and three two-coordinate S atoms are present.

This principle does become rather scholastic, however, in the hitherto unique case of a second modification of SrSi[208]. Figure 15 illustrates the isolated Si_{10} units occurring in the structure of this modification. Four three-coordinate, two two-coordinate, and four one-coordinate Si atoms are seen to be present. Calculation of the various formal charges from these coordination numbers indicates 20 negative charges for the overall Si_{20} unit which are compensated by 10 Sr "ions".

Assignment of the phase Sr_4Si_7[174] remains unclear. An ionic formulation indicates 1.14 negative charges on the Si atom. A structure of the α-$ThSi_2$ type is formed whose Si partial lattice is depicted in Figure 16. Stoichiometric

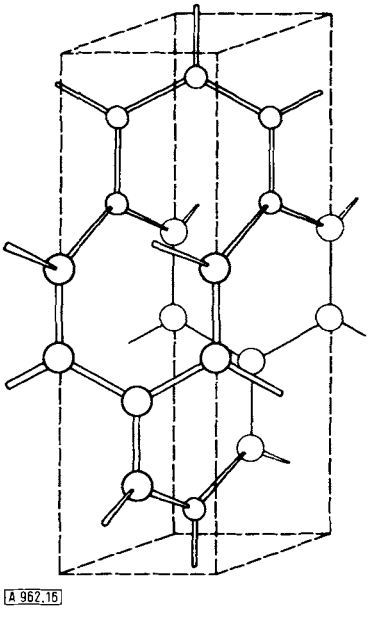

Fig. 16. Silicon partial lattice in α-$ThSi_2$ (after *A. F. Wells:* Structural Inorganic Chemistry. Clarendon Press, Oxford 1962).

deviation becomes possible because of disorder in the Si partial lattice. In this structure each Si atom has three nearest Si neighbors. The four atoms are located in a plane so that, as in $Ca_{0.5}Sr_{2.5}Si_4$ and in the second modification of SrSi, planar Si_4 groups appear as structural units. The spatial arrangement shown arises by linkage of such planar Si_4 groups mutually twisted through 90°. This spatial arrangement is built up by an eightfold equipoint which in the case of Sr_4Si_7 is statistically occupied by only seven Si atoms. This means that statistical divisions occur in the Si partial lattice which generate three two-coordinate Si atoms per isolated vacancy. The coexistence of two- and three-coordinate Si atoms is in harmony with

the calculated formal charge of between 1 and 2. However, there is no longer a clear-cut assignment in this case, particularly in view of a certain phase width, which is also a special feature of this compound.

4.3.2. Phases not Obeying the Zintl-Klemm-Busmann Concept

Apart from the phases corresponding to the extended Zintl-Klemm-Busmann concept there are others which do not fit into this scheme. They include phases in which the atomic ratio assumes values tending toward one extreme or the other.

a) Phases having a high content of electronegative element

Let us first consider phases particularly rich in electronegative elements. Of the phases with elements of Group IVB structures are available for the compounds Na_8Si_{46}[52], K_8Si_{46}[78,232], K_8Ge_{46}[78,232], K_8Sn_{46}[78], Na_xSi_{136}[52], and Li_2Sn_5[24].

The structure of the compounds Na_8Sn_{46} and K_8X_{46} (X = Si, Ge, Sn) can be described by analogy with the clathrates $8X{\cdot}46H_2O$ (Fig. 17) studied by *Claussen*[230] and by *Pauling* and *Marsh*. The Group IVB atoms occupy the positions of the water molecules. Twenty such atoms form a pentagonal dodecahedron. The unit cell contains two such dodecahedrons which are linked *via* six further Si, Ge, or Sn atoms in such a manner that six tetrakaidecahedrons per cell result, which are contained by twelve pentagonal faces in addition to two diametrically opposite hexagons. An alkali metal atom is located at the center of each of the tetrakaidecahedrons and the dodecahedrons leading to an atomic ratio of 8:46.

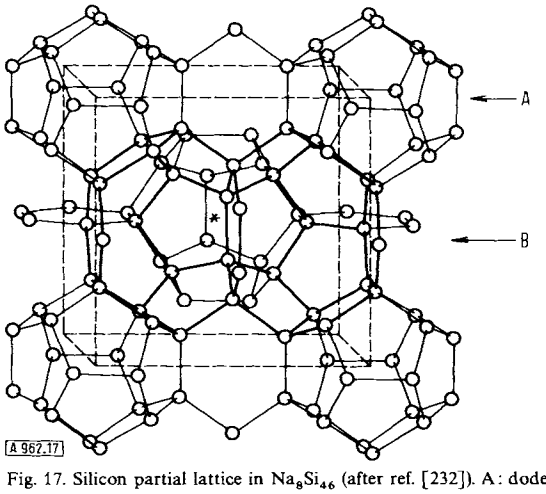

Fig. 17. Silicon partial lattice in Na_8Si_{46} (after ref. [232]). A: dodecahedron; B: tetrakaidecahedron.

Hagenmuller et al. have investigated a Na_xSi_{136} species[52]. Powder diagrams of this compound could be interpreted by assuming a clathrate-type structure corresponding to that of the gas hydrates $24X{\cdot}136H_2O$. The Si atoms again occupy the water-molecule sites and form a spatial network that likewise contains dodecahedrons and tetradecahedrons occupied to varying degrees by Na atoms. The element(IV) atoms in the two structures are surrounded approximately tetrahedrally by four close neighbors of the same species. The respective interatomic distances are only slightly greater than in the tetrahedral structure of the corresponding elemental lattices and the bonding angles approach the ideal tetrahedral angle to a greater or lesser extent.

In Li_2Sn_5[24] the partial Sn lattice consists of a spatial network which is however composed of six-coordinate Sn atoms (≙ coordination of the Sn atoms in white tin). Pentagonal parallel channels in which the Li atoms are fixed run through the structure (Fig. 18). The Sn—Sn distances are only slightly larger than in white tin (3.02 and 3.18 Å in white tin, 3.11 to 3.31 Å in Li_2Sn_5).

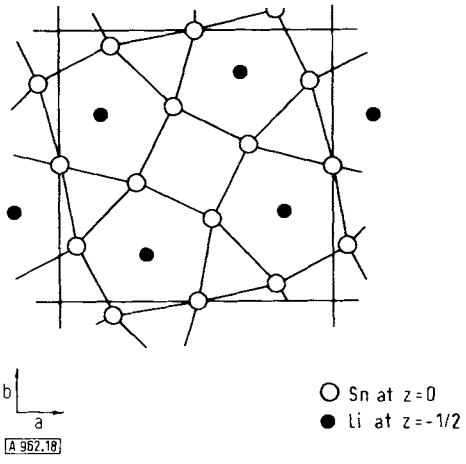

Fig. 18. Projection of the unit cell of Li_2Sn_5 onto the *a,b* plane (after ref. [24]).

b) Phases having a high content of electropositive element

Metallic structures with high coordination numbers were found by *Wölfel et al.* in $Ca_{33}Ge$ and Ca_7Ge[146]. The alkaline earth metal atoms are cubic close packed with superstructures imposed by the Ge atoms. The phases Ca_7Si, Sr_7Si, and Ba_7Si[147] are isotypic with Ca_7Ge.

Metallic structures are also found in the phases $Li_{22}Si_5$, $Li_{22}Ge_5$, $Li_{22}Sn_5$, $Li_{22}Pb_5$. They can be structurally related to the cubic space-centered cell of the lithium lattice itself. The lithium and element(IV) atoms are not however distributed randomly but an ordered atomic distribution is established which can be described to a first approximation as a cell with the sixfold axis of elemental lithium[9,26]. Studies on single crystals of $Li_{22}Si_5$ also revealed weak superstructure reflections which require a further fivefold increase in these cell constants[10]. Particularly striking is the valence electron concentration of these phases which is calculated as 21:13.5 and thus together with the structure found corresponds to the β-brass type of the Hume-Rothery phases. A similar observation is made for $Li_{10}Si_3$[13]. An atomic arrangement is also found here which has the unit cell of cubic space-centered lithium. Again the lattice constant of the lithium cell is multiplied to a first approximation by six so that the resulting cell contains 432 atomic positions. However, analysis and density and X-ray findings show only 416 sites to be occupied, *i.e.* there are 16 vacancies in the lattice. The valence electron concentration is found to be 21:12.4 and is thus close to the VEC of

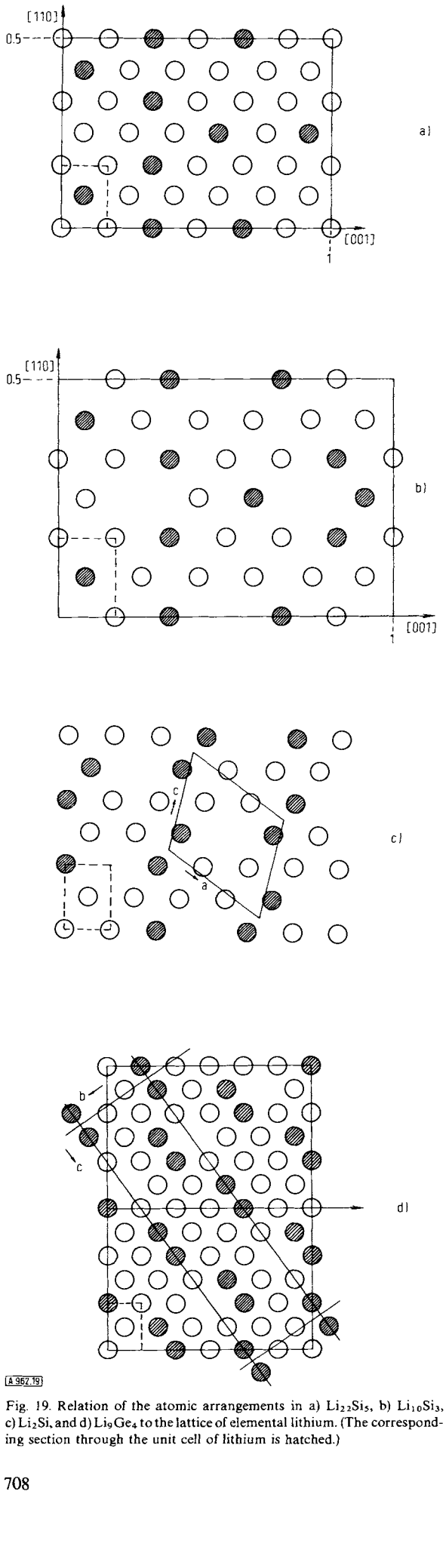

Fig. 19. Relation of the atomic arrangements in a) $Li_{22}Si_5$, b) $Li_{10}Si_3$, c) Li_2Si, and d) Li_9Ge_4 to the lattice of elemental lithium. (The corresponding section through the unit cell of lithium is hatched.)

the γ-brass phase which also has a corresponding number of lattice vacancies.

c) Other deviating phases

Metallic structures not obeying the Zintl-Klemm-Busmann concept are sometimes also found in compounds not having such extreme compositions. Thus *Ramsay* and *Zalkin*[27, 29] showed that all the stoichiometrically widely varying phases of the LiPb system can be structurally related to the cubic body-centered cell of elemental lithium. LiPb, Li_3Pb, and Li_7Pb_2, like $Li_{22}Pb_5$, contain isolated Pb atoms, *i.e.* only such as are surrounded by Li atoms, whereas Li_8Pb_3 contains an equal number of isolated Pb atoms and Pb_2 dumbbells. Dumbbells units of this kind are also present in Li_2Si[14] which can be described as monoclinic and, like the phases $Li_{22}Si_5$ and $Li_{10}Si_3$, can be related to the lattice of elemental lithium. Figures 19a—d provide a schematic illustration of the relationships between the structures of Li_2Si, $Li_{10}Si_3$, and $Li_{22}Si_5$, sections perpendicular to the face diagonals being shown for the structures of the last two compounds. Relative to the packing in elemental lithium 1/7 of all lattice sites in Li_2Si are vacant. In the real structure of course the atomic locations are distorted with regard to the positions in the ideal lithium lattice. This is even more the case in the structure of Li_9Ge_4[20], although the number of vacancies (1/10) is lower than in Li_2Si.

We also find a cubic closest packing with an ordered distribution of atoms in the Cu_3Au type in which the compounds Ca_3Pb[146], $CaPb_3$[153], $NaPb_3$[61], $CaSn_3$[151], Ca_3Sn[209], $CaTl_3$[153], $MgIn_{2.5}$[122], $SrBi_3$[171], Mg_3In (HT)[122], as well as $SrPb_3$[153] and $SrTl_3$[161], crystallize, both of the latter exhibiting tetragonal distortion.

The structures of the compounds $CaAl_2$[154], KBi_2[75], $RbBi_2$[69], $CsBi_2$[76], and KPb_2[85] show them to number among the Laves phases. Further variants of metallic lattices occur in particular with the compounds of alkali and alkaline earth metals with Group IIIB elements (Tables 1—9) which, however, will not be considered in detail within the framework of this report.

5. Discussion

A survey of the material available shows that most of the phases considered can be rationalized in terms of the extended concept due to *Zintl*, *Klemm*, and *Busmann*. It is, however, rather unsatisfactory that nothing can yet be said about the actual structures beyond the coordination of the atoms in the anion partial lattice. Thus the factors are still unknown which, for instance, determine which of the fundamentally feasible arrangements—layer structure, three-dimensional crosslinked structure, or isolated tetrahedrons—is formed *e.g.* in the series $CaSi_2$, $SrSi_2$, $BaSi_2$. Steric constants *e.g.* the size ratios of the atoms clearly play an essential role here, as has been underlined by attempts to incorporate barium into the $SrSi_2$ lattice in place of strontium[233]. It is also conceivable that the donor strength of the non-noble alloy component may

exert an effect. An influence of donor strength should also manifest itself in the bond lengths of the anionic partial lattice. Figure 20 represents a plot of the Si—Si distance in the silicides of formal charge 1−, for which the most experimental data has so far become available,

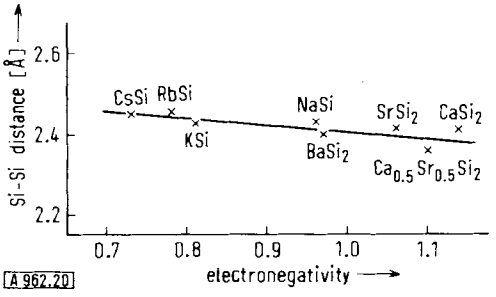

Fig. 20. Dependence of the Si—Si distance on the electronegativities of the alloy components (formal charge on silicon: 1 −).

versus the electronegativity of the electropositive alloy component. As the electronegativity increases a shortening of the bond lengths is seen to occur at the same coordination number (8—9). This is in full accord with the concept that the negative charge on the silicon partial lattice falls with decreasing donor strength of the alkali or alkaline earth metal and that the equally charged Si atoms are then subject to less mutual repulsion. Too few experimental data are available for more highly charged Si partial lattices to permit subscription to a similar view. In keeping with the higher formal charge, however, larger Si—Si distances are generally observed for a given coordination number.

Studies carried out in recent years, as shown above, have indicated that the validity of the extended Zintl-Klemm-Busmann concept is limited. It cannot be used in interpreting phases having atomic ratios tending to one extreme or the other. In both limiting cases the bonding state of the excess component dictates the crystal structure.

In addition, phases are also known which certainly fall within the province of the Zintl-Klemm-Busmann concept but whose anion lattices do not satisfy the $(8-N)$ rule.

A discussion of all these deviating phases reveals that the difference in electronegativity of the components is always particularly slight. This results either from the less pronounced electropositive character of the alkali or alkaline earth metal concerned—*e.g.* lithium or magnesium—or from the very low electronegativity of the anionic component—*e.g.* the heaviest elements of Group VB and IVB and all elements of Group IIIB. Both unfavorable features are frequently combined in the deviations. The extreme charge separation invoked by *Zintl*, *Klemm*, and *Busmann* loses all relevance and thereby its significance in determining the structure. The inadequacy of the extended concept is understandable in such cases.

Apart from the polar character of the classes of compounds discussed here, covalent binding contributions are also important in those phases having an associated anion partial lattice, as implicated by the validity of the $(8-N)$ rule. Within the anion partial lattice bond lengths are found experimentally which are comparable with those in the elemental lattices. The single-bond energies should therefore also play a determining role in the formation of these partial lattices. The single-bond energies of the Group IVB and VB elements are listed in Table 16. Most of

Table 16. Single bond energies for elements of Groups IVB and VB [235].

Bond	Bond energy [kcal/mol]	Bond	Bond energy [kcal/mol]
Si—Si	42.2	P—P	51.3
Ge—Ge	37.6	As—As	32.1
Sn—Sn	34.2	Sb—Sb	30.2
Pb—Pb	?	Bi—Bi	25

the phases deviating from the Zintl-Klemm-Busmann concept are indeed found with elements having a relatively low single-bond energy. The same conclusion can be drawn from the observation that the metallic bonding character increases on going from the top to the bottom of a group in the Periodic Table and in extreme cases, as for example those of white tin and lead, the element itself no longer conforms to the $(8-N)$ rule.

In spite of these limitations, it may be said that a fairly large group of compounds of the systems in question can be described by the extended Zintl-Klemm-Busmann concept. It appears an obvious step to utilize this description in a new definition of Zintl phases which embraces *Laves'* definition and, to a certain degree, the crystallographic definition: accordingly, the designation Zintl phases should apply to intermetallic compounds which display a pronounced heteropolar bonding contribution and in agreement with an ionic formulation in their anion partial lattices—if necessary after resolution of fractional charges into nearest integral values—obey the $(8-N)$ rule.

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Nuclear Medicine and Radiochemistry

By Hans Götte and Gerhard Kloss[*]

Dedicated to Professor Karl Winnacker on the occasion of his 70th birthday

Nuclear-medical diagnostic methods are widely used at present, examples being localization diagnosis *e.g.* of the thyroid, the kidney, and the spleen and function tests, *e.g.* on the thyroid and on the liver. For these tests it is essential to have organ-specific vehicle substances that can be labeled with suitable radionuclides. For *in-vivo* investigations, the exposure of the patient to radiation should be kept as small as possible, but the radiation must nevertheless be sufficient to allow the detection of the nuclide. Today, the therapeutic use of radionuclides is only small in comparison with their use in diagnosis.

1. Nuclear Medical Methods and Problems

1.1. *In-vivo* Methods

The possibility of using radioactive substances for the investigation of transport and distribution processes and of analytical questions has opened up previously inaccessible fields to the medical sciences. A new field of specialization, nuclear medicine, has arisen. This is a branch of science and clinical practice concerned with the diagnostic and therapeutic use of unsealed radioactive substances; at present, the number of uses in diagnosis is much greater than that in therapy.

Many of the diagnostic tests are *in-vivo* methods. They are based on the fact that some substances, when given *e.g.* by injection or orally, accumulate in certain organs. If compounds of this type can be labeled with γ-emitting radionuclides, they can be used as vehicles for the latter. It does not matter in principle whether the compound is labeled with a radioisotope of one of its component elements (isotope labeling) or with a non-isotopic radionuclide (foreign labeling or hetero-labeling). With the aid of special equipment, the scintigraph, it is then possible to record the distribution of the γ-quanta emitted by the radionuclides, *i.e.* to scan the distribution of the activity in the accumulating organ (Fig. 1).

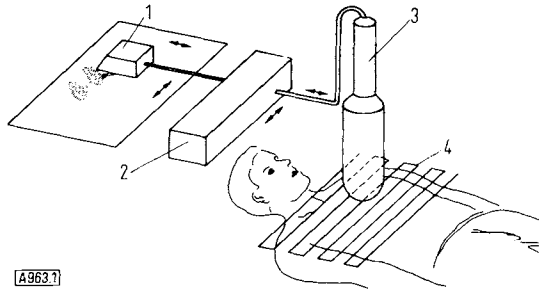

Fig. 1. Schematic diagram of the operation of a scintigraph: 1, point recorder; 2, amplifier; 3, scintillation counter; 4, collimator.

These activity diagrams are recorded by moving a mobile γ-radiation detector in a winding course over the organ in question. A point recorder moving at the same rate marks a point whenever the counter has recorded a certain pulse rate. If this pulse rate is not reached, the corresponding place on the recording paper is left blank. Instruments are also commercially available that print different colors according to the activity level, so that it is possible to distinguish stronger and weaker accumulation. Such scin-

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tigrams (or scans) can provide information on the existence of abnormalities in the storage properties of the organ in question. Morphological changes, *e. g.* some carcinomas, can be recognized in this way.

These localization tests are supplemented by function diagnosis, in which one measures the fraction of the labeled substance administered that is stored in the organ in question or excreted by it; the functioning of the organ can be deduced from the course of the curves. The radiation is detected by means of one or more fixed collimated detectors applied over the organ under investigation. The activity variation recorded by them is marked by a pen.

A gamma camera is used to follow rapid diffusion processes. This contains a large crystal with a collimator system between the crystal and the patient and a series of photomultipliers placed on the crystal. The activity distributions displayed on an oscillograph screen can be photographed at short intervals (function scintigraphy).

There are essentially three requirements that must be satisfied if a nuclear-medical preparation is to be suitable for such investigations, *i. e.* minimum exposure of the patient to radiation, harmlessness of the vehicle substance to the organism, and optimum diagnostic information.

For these reasons, a radiodiagnostic agent for *in-vivo* investigations should have the following properties:

1. To minimize exposure to radiation, as far as possible, the preparation should not contain particle emitters, since α- and β-rays give up all their energy in the tissue because of their short range; moreover, they make no contribution to the measurement. Preparations with radionuclides having short half-lives are preferred, but the half-life must be sufficiently long to guarantee that sufficient activity is still present for the measurement.

2. As far as possible, the radiodiagnostic preparation should be physiological, *i. e.* it should not cause any reactions in the organism nor should it be deposited as an exogenous substance. Unphysiological substances must be capable of being prepared with high specific activities so that after injection of very small quantities that are still tolerated by the organism without reaction, they are still sufficiently active for detection.

3. The radiodiagnostic preparation should be selectively accumulated by the organs or systems whose scintigrams are to be recorded or whose function is to be tested, since the radiation of radioactive material concentrated elsewhere interferes with the measurement.

4. To avoid chemical noxae, radiodiagnostic preparations whose residence time in the body is short, *i. e.* which are rapidly eliminated (unchanged or after metabolization), are preferred. However, the labeled vehicle substance must be stored as long as is necessary for the test.

5. The substance must also be isotopically and radiochemically pure. Thus it must contain only the desired radionuclide, and this must be present only in the desired chemical form.

6. The labeling must be stable both chemically and radiation-chemically *i. e.* toward its own radiation, so that no radioactive decomposition products occur. Moreover, the labeled molecule must not be changed by metabolic processes in the organism, unless the function test is based on such a biotransformation. If these stability conditions are not satisfied, labeled metabolites may appear in undesirable places and interfere with the measurement of the process or organ under investigation.

7. The radiation of the radionuclide used should be capable of being measured with high counting yields so that only a low activity need be administered, *i. e.* its γ-energy should be between 100 and 200 keV.

8. It must be possible to produce the preparations in a few steps, as far as possible by simple operations, at low cost, and in a pyrogen-free and sterile state.

These partly contradictory requirements are clearly often mutually exclusive. The ideal *in-vivo* radiodiagnostic preparation cannot exist. A compromise must be found in every case, and it is up to the nuclear physician to choose the most suitable of the available preparations.

The following examples are intended on the one hand to illustrate the type of problem that arises in nuclear medicine and to demonstrate the diversity of the methods used to deal with them. On the other hand, they are intended to show how much the required radioactive preparations can differ in their chemical composition and physical state, as well as to illustrate the degree to which it has so far been possible to satisfy the eight requirements by the use both of isotope-labeled and of hetero-labeled physiological and unphysiological substances.

1.1.1. Examples of Localization Diagnosis

Thyroid

Scintigrams of the thyroid are obtained after administration of radioactive iodide ions. Figure 2 shows the scintigram of a thyroid with a "hot" node such as appears for toxic adenomas, a palpable abnormality that was known earlier from pathological and anatomical investigations, but whose incidence and importance were recognized and its differentiation from other thyroid disturbances made possible only through nuclear medicine. It involves partly hyperfunctioning tissue that produces morbid states by over-production of thyroid hormones. It can be seen from Figure 3, on the other hand, that tissue that is incapable of storage, *i. e.* a "cold" node, is present here, and this points to a tumor.

Radioactively labeled iodine has partly ideal characteristics as a radiodiagnostic preparation for this diagnostic problem, since a physiological process, *i. e.* the absorption of iodide ions by thyroid tissue, is used to check this very process. Because of the long physical and biological half-life of I-131, which is the most commonly used isotope at present, radiation exposure must be taken into account.

Tc-99m has recently been used in the form of carrier-free pertechnetate for the investigation of the thyroid. This ion is absorbed by the thyroid in almost the same way as the iodide ion. The fact that investigations can also be carried out with pertechnetate shows that the diagnostic information can be obtained even under unphysiological conditions; the activity of the carrier-free technetium used, which is about 1 mCi (corresponding to 2×10^{-10} g), should not lead to any chemical damage, while the decrease in

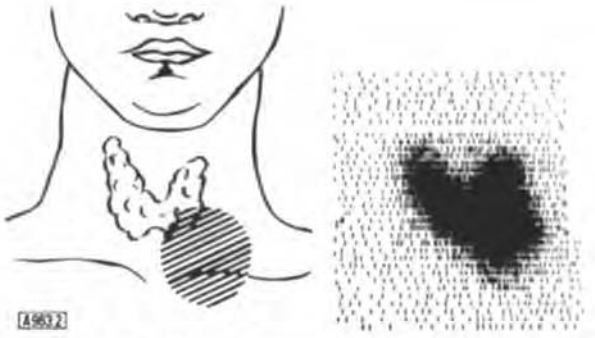


Fig. 2. Hot node; diagnosis: hyperfunction. Increased iodine storage in a node that enlarges the thyroid on the left. Schematic representation of the palpable node and scintigram.

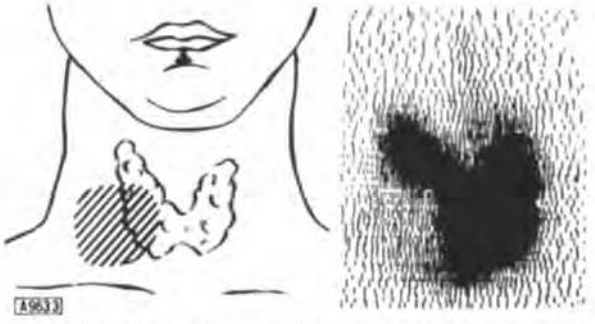
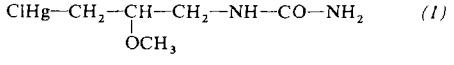


Fig. 3. Cold node; diagnosis: suspected carcinoma. Reduced iodine storage in a node that enlarges the thyroid on the right. Schematic representation of the palpable node and scintigram.

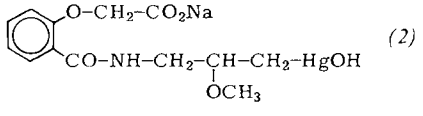
radiation exposure should be appreciable because of the short half-life of technetium.

Kidney

For the scintigraphic visualization of the kidneys, the nuclear physician has available three mercurial injection preparations with different physical and biological half-lifes: Hg-197- or Hg-203-labeled chlormerodrin *(1)* and Hg-203-labeled Salyrgan® *(2)*.



(1)



(2)

Use is made here of the well-known ability of the kidneys to accumulate selectively organomercury compounds and/or mercury liberated from them, *i.e.*, unlike in the preceding example, completely unphysiological compounds. An iron-ascorbic acid complex of unknown chemical structure that contains Tc-99m has recently also been placed on the market for this type of kidney investigation. This preparation is not only preferable because of reduced radiation exposure, but is probably also more physiological than the mercury compounds.

Lung

Scintigrams of the lung can be obtained with iodine-labeled protein particles. The aggregates measuring between 5 and 50 μm remain lodged in the capillaries only where the tissue is healthy. Regions with a disturbed blood supply are visible in the scintigram as light areas (Fig. 4); degenerate, *e.g.* carcinomatous, tissue can be detected in this way.

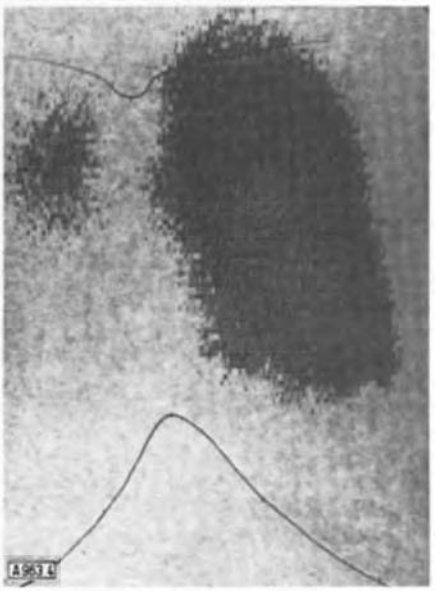
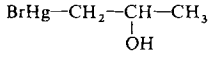


Fig. 4. Lung scintigram; extensive pathological findings. Only traces of functioning tissue remain on the right.

An unphysiological process is thus used here to scan an organ with a substance that can probably still be regarded as physiological. The protein particles have the advantage that they are broken down in the body with an average half-life of 4 to 6 hours, so that the capillaries again become permeable. From the medical point of view, this is an advantage over the use of an iron hydroxide sol labeled with In-113m, whose particles remain in the lung for a long time, even though the radiation exposure due to In-113m is less than that due to I-131.

Spleen

Erythrocytes labeled with Cr-51 and subjected to heat treatment or chemically damaged by labeling with BMHP-Hg-197 *(3)* can be used for the scintigraphy of the spleen.



(3)

The red blood cells, which are no longer capable of functioning, are filtered out of the blood stream and uniformly stored by the healthy spleen tissue, so that scanning becomes possible. Here again, therefore, use is made of a substantially physiological process: One uses the ability of the spleen to eliminate damaged erythrocytes, and the vehicle substance used is endogenous, but its physical behavior has been altered by hetero-labeling.

Brain

Scintigrams of brain tumors have recently been recorded mainly with Te-99m, again in the form of carrier-free pertechnetate. I-131-labeled albumin and the Hg-197-labeled

chlormerodrin mentioned in connection with kidney scintigraphy, as well as the EDTA complex of In-113m, have also been used for this purpose. The physiological properties thus evidently play a minor part if such different compounds have proved to be suitable vehicle substances. This is mainly because we are concerned here not with specific labeling of the tumor tissue but with portrayal of the damage caused by the tumor, *i.e.* the penetration of the blood-brain barrier, which can be recognized from the activity that diffuses into the pathological tissue.

1.1.2. Examples of Function Diagnosis

Thyroid

One of the earliest nuclear-medical tests, that of the thyroid, still occupies a dominant place among the function tests. The basis of the test is that the rate of absorption of carrier-free radioiodide ions by this organ is followed after oral administration, and deviations from normal values are recorded.

Liver

Function tests on the liver can be carried out with I-131-labeled Bengal rose. After intravenous injection of the preparation, the course of the activity is followed with shielded counters over the liver (uptake of activity) and over the head (escape of activity). Figure 5 shows how the absorption curves after administration of labeled Bengal rose differ according to the morbidity states of the liver (inflammations, blockage of the bile duct). The isotope-labeled compound is unphysiological, but is eliminated in a short time.

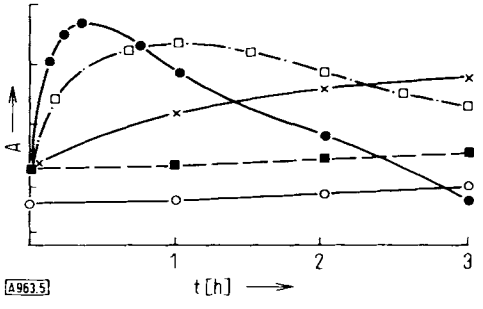
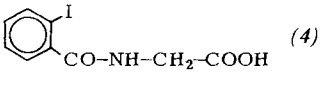


Fig. 5. Liver function test with I-131-labeled Bengal rose. ●···●, normal; □—□, partial blockage; ×—×, complete blockage; ■···■, acute hepatitis; ○—○, compensated cirrhosis.

Investigations on the function of the reticuloendothelial system of the liver can be carried out with colloidal gold having a particle size of 300 Å; it must be remembered, however, that gold remains in the liver for a time after the activity has decayed.

Kidney

To measure the kidney clearance, which is a quantity indicating how many milliliters of plasma are freed from ballast materials per unit time, I-131-labeled *o*-iodohippuric acid *(4)* is injected intravenously and the course of the activity is followed with a counter applied over the heart (Fig. 6). This concentration is proportional to the concentration C in blood.



(4)

During and after mixing in the blood circulation, the labeled substance does not remain only in the blood stream but partly penetrates into extravascular spaces, and is also eliminated *via* the kidneys.

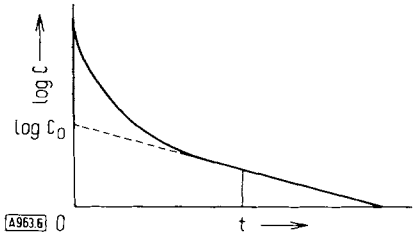


Fig. 6. Determination of the renal clearance with I-131-labeled *o*-iodohippuric acid *(4)*.

The part of the plot corresponding to this process is curved. Then, in a semilogarithmic plot, the concentration C decreases linearly, *i.e.* according to a uniform exponential function e^{-kt}. This means that an equilibrium prevails between the vascular and extravascular systems and the decrease in activity is then due to only one process, *i.e.* the renal clearance. Its value N_c can be calculated by determination of the half-life τ of the above process and the activity concentration C_t in a blood sample taken during the period of linear decrease (V = distribution volume in the body).

$$N_c = k \cdot V$$

$$-K = -\frac{\ln 2}{\tau};\ V = \frac{A_i}{C_0}$$

(A_i = activity injected)

Blood Volume

The function studies also include the determination of certain distribution volumes, particularly the blood volume. The methods are based on the dilution principle. To determine the blood volume, for example, a few ml containing a few μCi of I-131-labeled albumin or a suspension of erythrocytes labeled with Cr-51 and recently also transferrin labeled with In-113m, *i.e.* compounds that are unlabeled constituents of the blood and so do not leave the vascular system, are injected intravenously. The blood volume is calculated from their dilution after mixing in the body. Albumin hetero-labeled with I-131, like transferrin labeled with In-113m, behaves physiologically, since the labeling does not interfere with the properties of the protein in any case. Transferrin labeled with In-113m is the most favorable because of the short half-life of the nuclide, not only from the standpoint of radiation burden, but also because it allows the repetition of the determination at intervals of a few hours.

1.2. *In-vitro* Methods

In addition to the *in-vivo* methods, *in-vitro* methods that yield function-diagnostic information have recently also

been developed. Thus the binding capacity of a particular serum protein that binds thyroid hormones can be determined by addition of a known small quantity (about 0.01 ng) of radioiodine-labeled triiodothyronine to the serum and measurement of the fraction that is bound by the protein. The ratio of free to bound hormone allows conclusions to be drawn regarding hyperfunction, normal function, or hypofunction of the thyroid. The determination of these functional states, unlike the thyroid function test (with orally administered radioiodide ions), is achieved without any radiation exposure. This is a real advantage of the *in-vitro* method. Commercially available kits for such investigations contain the necessary reagents, the correct quantity of adsorbent, and 1 μCi of radioiodine-labeled hormone.

A more demanding method is that known as radioimmunoassay (Fig. 7)[1]. This is used for the determination of peptide hormones, *e.g.* insulin or growth hormone, as well as of other substances in human serum in the ng/ml range. The analytical method is based on the immunological reaction between antigen and antibody. The antibody is produced by injection of unlabeled polypeptide hormone, *e.g.* human insulin, into an animal, *e.g.* a rabbit or a guinea pig. An antibody is produced in the serum of the host organism within a few weeks. This antibody is capable of binding the antigen, *i.e.* the hormone, when the serum containing the antibody is mixed *in vitro* with another, *e.g.* human serum containing the antigen. This reaction proceeds slowly; the free antigen can be selectively separated from a solution that contains both the antigen-antibody reaction product and the free antigen by adsorption, *e.g.* on Amberlite.

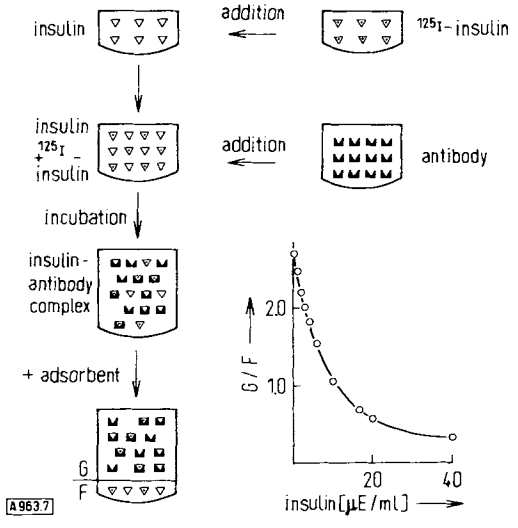


Fig. 7. Schematic representation of the principles of radioimmunoassay with the determination of insulin as an example. Bottom right: calibration curve. G = bound insulin, F = free insulin.

If the hormones to be determined can be labeled with radioiodine (polypeptides containing tyrosine or histidine can be iodinated and hence hetero-labeled with radioiodine), the quantities of antibody-bound hormone and of free hormone can be determined by simple measurement of the activity of the adsorbent and of the supernatant. The content of peptide hormones in the serum of a patient is determined with the aid of a calibration curve.

2. Functions of Radiochemistry in Nuclear Medicine

Nuclear medicine is closely linked with radiochemistry. The latter is responsible on the one hand for the routine production of the preparations required in nuclear medicine, *i.e.* the transformation of the radionuclides into the chemical and physical form suitable for use by the physician, while on the other hand, it is involved in the improvement of existing preparations and in the development and discovery of new labeled preparations. Its functions are thus primarily preparative. Starting from about 15 radionuclides that are important in nuclear medicine, more than 40 preparations (of very different types, as can be seen from Table 1) are prepared on a routine basis, about one third of these being isotope-labeled and two thirds hetero-labeled.

Table 1. Important nuclear-medical preparations in order of increasing half-life (τ).

Radionuclide	τ [d]	Vehicle substances
Indium-113m	0.07	transferrin, indium-EDTA complex
Technetium-99m	0.25	pertechnetate, iron-ascorbic acid complex, sulfur colloid
Copper-64	0.5	copper-EDTA complex
Mercury-197	2.7	chlormerodrin *(1)*, 1-bromomercuri-2-propanol *(3)* (BMHP)
Gold-198	2.7	colloidal gold, 5 or 30 nm
Molybdenum-99	2.8	^{99}Mo-^{99m}Tc generator
Xenon-133	5.6	dissolved in physiological saline
Iodine-131	8.05	albumin, *o*-iodohippuric acid *(4)*, insulin, iodoinsulin, triolein, thybon, L-thyroxine, iodoalbumin, Bengal rose, albumin particles 5—50 μm, sodium iodide
Phosphorus-32	14.3	sodium phosphate, tri-*n*-octyl phosphate (in lipiodol)
Chromium-51	28	chromium albumin, chromium-EDTA complex, ^{51}Cr-labeled erythrocytes
Ytterbium-169	30	ytterbium-EDTA complex
Mercury-203	47	Salyrgan *(2)*
Iodine-125	60	albumin, *o*-iodohippuric acid *(4)*, insulin, placenta hormone, growth hormone
Selenium-75	127	2-amino-4-(methylseleno)butyric acid (selenomethionine)
Cobalt-57 and Cobalt-58	270 and 71 resp.	vitamin B_{12}

2.1. Labeling Methods

The radioelement most commonly used in nuclear medicine is radioiodine, and this is followed by Tc-99m, Au-198, and the mercury isotopes 197 and 203. Depending on the half-life of the radionuclides, the nuclear-medical preparations containing them must be freshly prepared at regular intervals. The labeling with radionuclides may be

carried out by isotope exchange or by chemical synthesis. Isotope exchange can be used when the substance to be labeled is readily obtainable in the inactive form and conditions favorable for the exchange, *e.g.* temperature and exchange rate, can be found. This is so *e.g.* for Bengal rose and thyroxine, both of which are labeled with elemental I-131. The starting material must be free from iodinatable or already iodinated compounds whose exchange rates are roughly equal to or greater than the rate of the desired reaction. For preparative purposes, the isotope exchange method is largely confined to the elements bromine and iodine.

Important examples of isotope-labeled compounds obtained by chemical synthesis are I-131-labeled triiodothyronine, which is obtained by iodination, and the mercury-containing preparations BMHP *(3)*, chlormerodrin *(1)*, and Salyrgan *(2)*, which are obtained in one step by addition of radioactively labeled mercury acetate to CC double bonds.

Hetero-labeling is particularly interesting in nuclear medicine, since among other things it allows the radioactive labeling of existing endogenous substances or substances that behave physiologically but cannot be obtained synthetically in the isotope-labeled form. An important condition for the use of a hetero-labeled substance in many cases is that its properties are not affected by the incorporation of the non-isotopic radionuclide. This is frequently the case *e.g.* for hetero-labeled proteins, whose molecules should not differ in their physiological properties or in their immunological behavior from corresponding unlabeled molecules.

The larger the molecule to be hetero-labeled, the smaller is the probability that the introduction of atoms of an element that does not occur in the molecule will affect the properties of the compound. Proteins with molecular weights of between 1000 and a few million are therefore generally found to be favorable for hetero-labeling, whereas interfering changes are brought about in small molecules.

From these standpoints, the great importance of the two radioisotopes I-131 and I-125 in thyroid diagnosis and therapy and in connection with kidney clearance is not entirely due to their nuclear-physical qualities (half-life, radiation energy). Because of its chemical properties, radioiodine is used more often than other radioelements for the hetero-labeling of biological substances, particularly of proteins. There is frequently no detectable difference in chemical, biochemical, or immunological behavior between labeled and unlabeled molecules if less than 1 atom of iodine/protein molecule is introduced during the iodination and if mild reaction conditions can be maintained.

The substitution of hydrogen in these reactions takes place as follows:

$$RH + I_2^* \leftrightarrow RI^* + HI^*$$

Half of the activity used is liberated as hydrogen iodide; more than 90% of the radioiodine can thus be economically used only if the hydrogen iodide is converted back into iodine by oxidizing agents such as *N*-chlorotoluenesulfonamide, nitrous acid, or a peroxy compound. However, these hard reaction conditions are not tolerated by all proteins. In addition to the desired molecules that are unchanged by the labeling, damaged molecules are then also formed, and these must be separated by chromatography and electrophoresis. This also applies to the radiation-chemical decomposition products that are formed at high specific activities as a result of the natural radiation of the labeled substances.

The proteins radioiodinated in this way include I-131-labeled human albumin for the determination of blood volumes. This product is also used as the starting material for another diagnostic preparation, I-131-labeled albumin particles. To prepare these, I-131-labeled albumin is precipitated in the form of aggregates by heat and pH changes. The size of these particles can be varied by adjustment of the reaction conditions.

Some nuclear-medical preparations must be prepared by biosynthesis, since chemical synthesis would be too expensive. This is so *e.g.* of vitamin B_{12}, which is obtained from the metabolic products of microorganisms whose culture media contain Co-57 or Co-58.

2.2. Generators

The loss of activity during transport between the manufacturer of the nuclear-preparations and the user is important in the case of radionuclides with half-lives of less than 10 h unless the two establishments are situated close together. This difficulty can be overcome in some cases by the use of radionuclide generators. These instruments, which are also known as milking systems, allow the repeated separation of a short-lived daughter nuclide from a longer-lived parent nuclide with a high separation factor (10^6—10^8) by a simple chemical operation, so that the short-lived radionuclide obtained can be brought into the

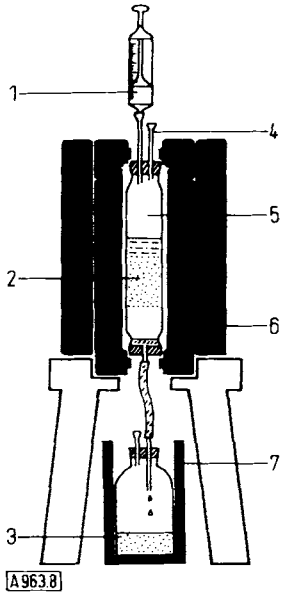


Fig. 8. Principle of a radionuclide generator: 1, syringe with sterile eluent solution; 2, sterilized adsorbent and parent nuclide; 3, sterile eluate with daughter nuclide; 4, deaeration cannula; 5, column replaceable after decay of the parent nuclide; 6, 7, lead shielding.

appropriate form for nuclear-medical use on the spot. The operation of such a generator is illustrated in Figure 8.

The longer-lived parent nuclide is supplied on an adsorbent in an elution column, which is closed at both ends with rubber caps. Elution is carried out by piercing these rubber caps with cannulas and injecting the elution liquid into the column. Before further treatment, the eluate is collected in a sterile receiver, also with a rubber cap.

Among these systems, the most important pairs for nuclear medicine are Mo-99/Tc-99m and Sn-113/In-113m. Technetium may be eluted in the form of carrier-free pertechnetate with isotonic salt solution and used in this form, or technetium-labeled sulfur colloid obtained from thiosulfate solution by acidification in the presence of the pertechnetate eluate may be used. The Tc-99m-iron-ascorbic acid complex can also be obtained by mixing the generator eluate with the dissolved complexing agent.

In-113m, which is obtained in the form of a hydrochloric acid eluate, is used *e.g.* for the labeling of transferrin, a protein of the globulin fraction that contains iron. The bonding of the indium to the protein is very strong; indium can evidently occupy the sites that are capable of accommodating iron. The eluate is adjusted to a certain pH value with sodium hydroxide solution and an amino acid and mixed with a transferrin solution such that one atom of radioindium is present per 50 protein molecules; there is no detectable difference in the behavior of labeled and unlabeled transferrin.

To make it easier for a nuclear physician to produce the radio-diagnostic preparations labeled with Tc-99m or In-113m kits containing all the reagents in the correct quantities and concentrations have been developed.

The extensive use of such short-lived radionuclides enables the need for minimal body burden on the patient to be largely satisfied. The importance of radionuclide generators in nuclear medicine is therefore steadily increasing. At a rough estimate, more than 10000 radionuclide generators are used annually in hospitals in the German Federal Republic.

The routine production and supply of radioactive preparations is always a race against time. It calls for precise cooperation between institutions of very different kinds. Because of the limited life of the nuclides, each step in the production cycle must be fitted to the next with very

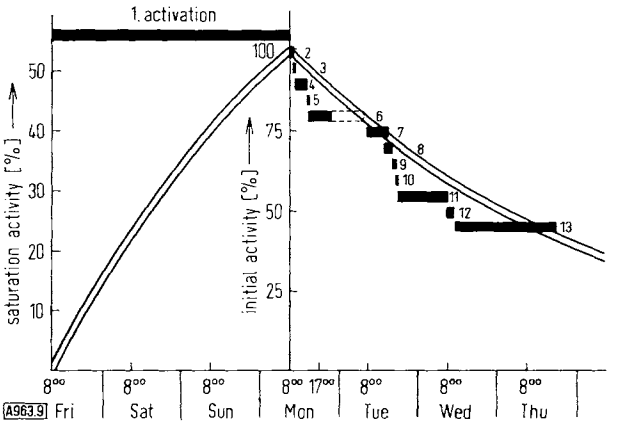


Fig. 9. Variation of activity during and after reactor irradiation of Hg-196 in the production and transport of Hg-197-labeled preparations.
The half-life of mercury-197 is 65 h. 1, activation; 2. discharge and transfer to containers; 3, transport from reactor to station (airport); 4, rail transport (air transport); 5, transport from station to radiochemical laboratory; 6, synthesis; 7, quality control; 8, dispensing; 9, packaging; 10, transport to carrier; 11, rail transport or air transport; 12, delivery; 13, use in the clinic.

little latitude and without loss of time. Figure 9 shows the time required for each step of the process in the synthesis of preparations containing Hg-197 (half-life 65 h) and the fraction of the activity produced that is present at the end of each step if no complications arise. No more than half of the activity produced in the reactor is available to the nuclear physician in this case.

In practice, it is necessary to allow for accidents and difficulties due both to technical factors and to the fact that up to six independent organizations are involved in the twelve steps; these include the reactor station, carriers, in some cases customs, production sites, and shipping agency. Ice and fog can also cause considerable interference.

Table 2 presents a survey of the starting activities and the corresponding, often invisible quantities that must be handled in syntheses in radiochemical laboratories. Fractions of these quantities could endanger both the personnel and the quality of the products if scattered around in an uncontrolled manner.

A condition that makes both synthesis and dispensing more difficult is the need to prepare many substances under aseptic conditions. A compromise is necessary in this case. Radiation protection calls for the use of pressures below atmospheric so that no radioactive material can

Table 2. Production processes for the most important radionuclides as well as activities and corresponding quantities handled in the preparation of radioactive drugs.

Radionuclide	Half-life	Production process	Activity per batch [Ci]	Quantity of radionuclide per batch [g]
Molybdenum-99	2.8 d	$[n\gamma]$	30	≈ 5
Technetium-99m	6.0 h	$^{98}Mo\ [n\gamma]\ ^{99}Mo \xrightarrow{\beta^-} {}^{99m}Tc$	30	$\approx 6.6 \times 10^{-6}$
Tin-113	115 d	$[n\gamma]$	1	$\approx 10^{-1}$
Indium-113m	1.7 h	$^{112}Sn[n\gamma]^{113}Sn \xrightarrow{\beta^-} {}^{113m}In$	0.1	$\approx 5.9 \times 10^{-9}$
Iodine-125	60 d	$^{124}Xe[n\gamma]^{125}Xe \xrightarrow{\beta^+} {}^{125}I$	0.1	$\approx 1 \times 10^{-5}$ (+0.001 g carrier)
Iodine-131	8.05 d	$^{130}Te[n\gamma]^{131}Te \xrightarrow{\beta^-} {}^{131}I$	2	$\approx 2 \times 10^{-4}$ (+0.001 g carrier)
Mercury-197	2.7 d	$[n\gamma]$	10	$\approx 5 \times 10^{-4}$ (+0.1 g carrier)
Gold-198	2.7 d	$[n\gamma]$	20	$\approx 1.5 \times 10^{-1}$
Mercury-203	47 d	$[n\gamma]$	2	≈ 1—2

escape, whereas sterile boxes should be under a pressure above atmospheric so that no non-sterile dust can enter them.

The synthesis is followed by quality control. It is first necessary to establish whether the preparation produced is contaminated with other radionuclides. It is then necessary to check whether the products are radiochemically pure. Moreover, the substances must be examined to see whether they contain pyrogens. This can usually be established during the few hours between the end of the synthesis and despatch. According to the pharmacopeias, sterility testing takes a very much longer time (ten days), and there is no time to wait for the results in the case of short-lived preparations. Here again we have two conflicting requirements, *i. e.* the desire for short-lived preparations to minimize the radiation exposure of the patient and the need to possess evidence of the sterility of the preparation at the time of delivery. In any case, the sterility of every batch must checked over the required period so that all those who have taken delivery of material from a given batch can be warned as soon as signs of non-sterility appear, and also to obtain an indication of the cause in the event of any accidents.

3. Research and Future Development

The second function of radiochemistry in nuclear medicine is in the field of development and research. Two lines of work can be distinguished here. One is concerned with the improvement of existing diagnostic possibilities, *i. e.* with the search for substances that are superior to those already in use with regard to organ-specific storage and also with regard to stability and physiological behavior as well as biological and physical half-lives. The other line is concerned with the fundamental investigation of new diagnostic problems.

3.1. New Radionuclides

It does not appear that the application of hitherto unused radionuclides for *in-vivo* methods could open up entirely new areas of diagnosis. On the other hand, it is conceivable that the use of some radionuclide that has not been employed in the past might lead to improvements. This category includes *e. g.* I-123, a 0.16 MeV γ-emitter with a half-life of 13 h. In thyroid diagnosis, this radioisotope would lead to a decrease in body burden by a factor of about 50 in comparison with I-131. However, its production requires the use of a cyclotron, and is therefore expensive. Moreover, owing to its short half-life, this isotope of iodine cannot be used for all thyroid investigations.

3.2. New Substances

Regarding the search for new substances with interesting physiological and chemical properties there is little evidence, as the examples listed in Table 1 have shown, that would allow the prediction of what type of compound might achieve importance in nuclear medicine. The known radiodiagnostic and radiotherapeutic preparations belong to such diverse classes of substances and exist in so many forms that this hardly offers a pointer for planned research. A brief glance at the history of the development of the principal radiodiagnostic preparations shows that while some of the nuclear-medical preparations were discovered as a result of deliberation, others were found by purely empirical research or even by accident. To take an extreme example: Who could have foretold in 1937, when *Segrè* discovered technetium—an element not existing on the earth, but which can be man-made—that its isotope 99m would be one of the most widely used radionuclides in nuclear medicine[2], or indeed that pertechnetate accumulates in the thyroid?

The use of radioiodine for thyroid diagnosis, on the other hand, was a follow-on from general medicine, so that *Hertz*, *Roberts*, and *Evans* were able to carry out the first nuclear-medical investigations in 1938[3]. Since *o*-iodohippuric acid has been in use for a long time as a contrast medium in X-ray diagnosis, *Tubis* labeled this substance with radioiodine for the first time and used it for the testing of kidney function[4]. Similar considerations led to the labeling of mercury-containing diuretics, *e. g.* Salyrgan, with radiomercury to allow the scintigraphic examination of the kidney. The use of particles of denatured protein in nuclear medicine is again the result of deliberation; however, chance also played a part in this case. *Taplin* first prepared these particles as a more physiological substance to replace radiogold colloid in liver diagnosis. His first experiments surprisingly gave good scintigrams of the lungs[5]; the particles were too large to pass through the lungs. A radiodiagnostic preparation for the lungs had thus been discovered. Smaller particles were suitable for the investigation of the liver.

Clues arising from general medicine will probably no longer be very helpful in the search for radiodiagnostic preparations. Recent preparations have been developed from biological considerations based on observation. One such preparation is transferrin labeled with In-113m. It was observed that carrier-free In-113m injected into the blood stream became bound to the plasma transferrin and so behaved as a chemically similar element to iron even *in vitro*.

However, an opportunity to find compounds that would be of interest in nuclear medicine has had to be ignored for years on economic grounds. Hundreds of thousands of chemical compounds are examined for possible activity in animal experiments in pharmacological laboratories throughout the world. If no such activity is found or if the test animal dies, the carcass is disposed of without examination to establish the organ in which the chemical compound administered or its metabolites have accumulated. It is conceivable that pointers for research with a definite purpose are lost forever here. There is a reasonable probability that compounds that behave organ-specifically would be found, and one would thus have a preliminary selection of substances that could be hetero-labeled and tested for use in nuclear medicine.

As evidence that there could be treasures in store here, one need only recall the circumstances involved in the

introduction of BMHP labeled with radiomercury as a radiodiagnostic preparation in 1963. The corresponding iodine compound had been prepared for the first time by *Sand* and *Hofmann* in 1900[6]. In 1957, it was examined by *Kessler et al.* for its diuretic action[7]. No such action was found, but the authors pointed out that the iodine compound accumulated to an unusual extent in the spleen. A few years later, on the basis of this result, *Wagner et al.* started to examine BMHP successfully for its properties as a radiodiagnostic preparation for the scintigraphy of the spleen[8].

3.3. Improvements to Known Diagnostic Methods

In attempts to improve radiodiagnostic preparations, the direction in which the search should be made is frequently indicated. The gold sol containing Au-198 that is used for liver diagnosis, which emits β- and hard γ-rays, leads to an appreciable radiation exposure of the liver. Moreover, the unphysiological colloidal gold remains in the organ under investigation after the activity has decayed, its elimination half-life being ≈ 30 days. I-131-Albumin particles, on the other hand, for roughly the same radiation exposure, are broken down with a half-life of 1—6 h. A sulfur colloid labeled with the shorter-lived (half-life 6 h) soft γ-emitter Tc-99m allows a considerable reduction of the radiation dose. It is necessary here to take into account the fact that colloidal sulfur is eliminated with a half-life of 25 days. Another aim will be to find a physiological substance that can be labeled with In-113m and is eliminated in a few hours. A preparation recently developed for lung investigations by several groups of workers consists of inactive particles that are labeled at the actual place of use with Tc-99m or In-113m from a milking system. The improvement in quality consists in the smaller radiation burden in comparison with particles labeled with radioiodine and in the fact that the previously prepared particles can be produced with greater uniformity.

3.4. Outlook

It still remains to be seen whether and to what extent the number of questions that can be answered by nuclear-medical means, as far as *in-vivo* methods with γ-emitters are concerned, will continue to increase in the future. The number of organs and hence the number of morbid states that can be examined is obviously limited. Since there are only a few organs that cannot be examined with the aid of the radiodiagnostic methods now available (these include the adrenal, the prostate, and the parathyroid), nuclear medicine will one day reach a limit in this direction. The same is true of efforts to improve existing diagnostic methods.

On the other hand, there still remains the fascinating problem, which overshadows all others, of finding substances with specific affinity for tumors, which, when radioactively labeled, would allow the localization of a wide variety of tumors and, if possible, that would also allow radiation therapy. If this could be achieved, α-emitters would also be of great importance in nuclear medicine, since their action could be confined to the region of the tumor because of their short range.

Thus if it appears that nuclear medicine is subject to certain limits insofar as γ-emitting radionuclides are used for *in-vivo* investigations, it will seem to the chemist that the use of the soft β-emitters H-3, C-14, and S-35 could open up new fields here. These pure β-emitters have only short ranges (less than 20 mg/cm^2); consequently, they cannot be detected outside the organism after incorporation, but can only be measured in excreta, body fluids, and tissue samples after suitable preparation. Investigations with H-3-, C-14-, and S-35-labeled compounds are therefore suitable for the study of metabolic processes, whose products can be detected and identified in the body fluids mentioned or in the respiratory air. Figure 10 shows the autoradiogram of a two-dimensional thin layer chromatogram of a urine extract from a test animal fed with a C-14-labeled chemically uniform pharmaceutical.

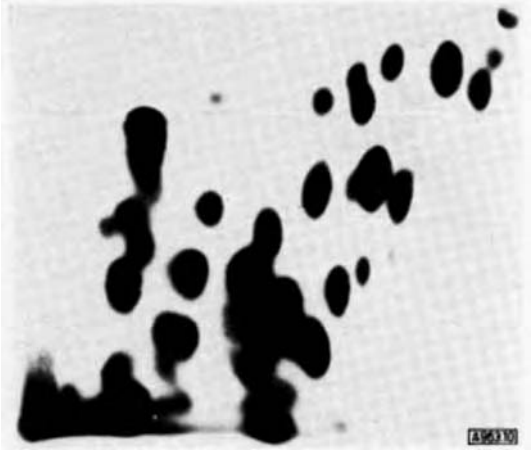


Fig. 10. Autoradiogram of a thin layer chromatogram of a urine extract from a test animal previously fed with a C-14-labeled pharmaceutical.

It is conceivable that this metabolite pattern will show characteristic changes as a result of a morbid process in the organism. If relationships could be demonstrated between abnormalities in the metabolism and morbid states, the three soft β-emitters should considerably extend the possibilities of nuclear-medical *in-vitro* investigations.

Interest in nuclear medicine has recently also been focused on the short-lived positron emitters produced by nuclear processes in the cyclotron. In particular, C-11 with a half-life of 20 minutes is becoming increasingly important. Fast methods for the synthesis of C-11-labeled carboxylic acids and suitable measuring equipment allow the deduction of information on the fate of these substances in the animal organism[9, 10].

The development of *in-vitro* methods must be considered apart from these aspects. The most important of these at present are the methods for the determination of peptide hormones on a radioimmunological basis. These will undoubtedly be applied to other substances, *e.g.* the prostaglandins and the steroids, and to the detection of drugs in the body. A special advantage of these methods is that, in principle, it is possible to automate them. The labeling

required for the *in-vitro* methods will not remain confined to radioiodine; radioimmunoassays based on tritium-labeled compounds are already well known. Whether it will be possible to use other radionuclides such as P-32 or S-35 without carriers (because of the high detection sensitivity required) is a question for preparative radiochemistry.

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Chemistry and Significance of the Carbohydrate Moieties of Human Serum Glycoproteins

By Karl Heide and Hans-Gerhard Schwick[*]

Dedicated to Professor Karl Winnacker on the occasion of his 70th birthday

The glycoproteins exercise important biological functions as transport proteins, inhibitors, enzymes, hormones, complement factors, and immunoglobulins. Their chemistry is characterized by a number of rules. Thus only asparagine, threonine, or serine can carry the oligosaccharide groups; for the *N*-acylglycosylamine linkage involving asparagine, the grouping Asn-X-Thr or Asn-X-Ser is always present in the peptide chain. However, practically no agreement is found in the molecular weights of the glycoproteins, their carbohydrate contents, and the relative contents of the various sugars. The biological significance of the carbohydrate fraction has not yet been explained, but some idea of the part played by the easily removable neuraminic acid is being formed.

1. Introduction

Glycoproteins occur widely in nature. They consist of a protein component and sugars covalently bonded to it; by definition, these sugars should not be nucleic acids. We are interested here only in the glycoproteins of human blood plasma[1–7]. Numerically they constitute the major part of the plasma proteins, since out of the 60 or so proteins that have been well characterized and isolated in the pure form, only albumin, retinol-binding protein[8], and a few trace proteins are free from carbohydrates (Table 1). Quantitatively, on the other hand, because of the abundance of albumin, which constitutes more than 50% of the total protein, the carbohydrate-free proteins predominate.

Table 1. Carbohydrate-free human serum proteins. (The serum contains about 43% of glycoproteins and about 57% of carbohydrate-free proteins.)

Protein	Amount present in serum [mg/100 ml]
Albumin	4400
Retinol-binding protein	5
C-reactive protein	< 1
Lysozyme	1
α-Amylase (B) (saliva)	
Carboanhydrase	

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2. Chemical Composition and Structure of the Glycoproteins

2.1. Carbohydrate Content of the Glycoproteins

The sugar units found in the glycoproteins are *N*-acetylglucosamine, *N*-acetylgalactosamine, galactose, mannose, glucose, fucose, *N*-acetylneuraminic acid (sialic acid), and xylose. They were formerly determined by the modifications of known methods described by us[9]: galactose and

mannose by the orcinol method of *Sörensen* and *Haugaard*, hexosamine with *p*-dimethylaminobenzaldehyde in *Blix*'s modification of the method of *Elson* and *Morgan*, acetylneuraminic acid with *Bial*'s reagent by *Klenk*'s method, and fucose by the cysteine-sulfuric acid method of *Dische* and *Shettles*.

It has recently become possible to detect the sugars and to determine them quantitatively by improved chromatographic techniques[10–13]. Glucosamine and galactosamine are determined in the amino acid analyzer[14]. Neuraminic acid is usually determined by the thiobarbituric acid method[15]. *o*-Phenanthroline, which forms a colored complex with bound neuraminic acid without any pretreatment, has recently been recommended[16].

The carbohydrate contents of a series of human plasma proteins are shown in Table 2. Detailed data are also available for a number of plasma proteins (Table 3). The contributions of the various sugar units to the total carbohydrate content are shown in Table 4 (Ig = immunoglobulin).

Glycoproteins for which such detailed analyses have not yet been carried out are particularly the complement factors C5[47] and C9[48] and the lipoproteins. We were the first, in 1957, to detect carbohydrates in the lipoproteins[49],

Table 2. Carbohydrate content of human plasma proteins.

	Mol.-wt.	Hexoses [%]	Ac-hexosamine [%]	Ac-neuraminic acid [%]	Fucose [%]	Total [%]	Ref.
Prealbumin	50000	0.4	—	—	—	—	[7]
α_1-Antitrypsin	54000	5.0	3.6	3.4	0.2	12.2	[17]
Prothrombin	60000	4.6 (2.8)	2.9 (3.1)	4.2 (2.3)	—	11.7	[18]
α_1B-Glycoprotein	50000	4.8	4.4	3.7	0.4	13.3	[7]
Transcortin	55700	5.4	4.7	3.2	0.8	14.1	[7, 19]
α_1T-Glycoprotein	60000	5.5	4.5	3.4	0.3	13.7	[7]
α_1-Antichymotrypsin	68000	9.9	7.4	6.6	0.7	24.6	[17]
9.5S-α_1-Glycoprotein	308000	5.5	3.7	3.5	0.1	12.8	[20]
Gc-Globulin	50800	2.0	2.0	0	0.2	4.2	[7]
Inter-α-trypsin inhibitor	160000	3.1	3.2	2.0	0.1	8.4	[17]
Uric-acid-binding α_1-α_2-globulin						12.1	[21]
Antithrombin III	65000	6.2	4.1	3.1		13.4	[17]
Zn-α_2-Glycoprotein	41000	7.0	4.0	7.0	0.2	18.2	[17]
α_2-HS-Glycoprotein	49000	5.2	3.9	4.1	0.2	13.4	[17]
C1-Inactivator	104000	10.8	9.2	14.3	0.4	34.7	[17]
Histidine-rich 3.8S-α_2-glycoprotein	58500	6.4	4.4	3.5	0	14.3	[22]
Serum cholinesterase	348000	9.3	8.4	6.0	0.2	23.9	[23]
Plasminogen	81000					1.45	[24]
4S-α_2-β_1-Glycoprotein	60000	10.7	9.0	7.5	0.5	27.7	[25]
8S-α_3-Glycoprotein	220000	11.0	10.8	9.2	0.4	31.4	[26]
β_1C-Globulin (C3)	185000	1.8	0.48	0.45	0.16	2.73	[27]
β_1E-Globulin (C4)	230000	1.9	1.4	1.0	0.1	4.3	[28]
Fibrinogen	341000	1.1	1.0	0.7	0	2.8	[7]
Antihemophilic globulin (F VIII)	2×10^6 (240000)		2.8				
Factor XIII	340000	1.9	1.6	1.2	0.2	4.9	[29]
β_2-Glycoprotein I	40000	7.8	6.2	4.5	0.3	18.8	[7]
C3-Activator / β_2-Glycoprotein II	60000	2.2	1.8	1.5	0.2	5.7	[30]
β_2-Glycoprotein III	35000	2.5	2.0	5.5	0.1	10.0	[31]
IgG-Globulin	150000	1.1	1.3	0.3	0.2	2.9	[32]
IgA-Globulin	160000 (aggr.)	3.2	2.3	1.8	0.2	7.5	[7]
IgM-Globulin	900000 (aggr.)	5.4	4.4	1.3	0.7	11.8	[32]
IgD-Globulin [mol/mol]	166000	47	36	15	0.5	11.3	[33]
IgE-Globulin [mol/mol]	190000	53	36	18	4	11.4	[34]

Table 3. Carbohydrate contents of some human serum glycoproteins.

	Hexoses [%]			Ac-hexosamine [%]	Ac-neuraminic acid [%]	Fucose [%]	Xylose [%]	Total [%]	Ref.
	Gal	Man	Glu						
α_1-Fetoprotein	0.49	0.68		0.89	1.3	+		3.36	[35, 36]
α_1-Acid glycoprotein	7.6	5.5		13.2	10.9	0.7	+	37.9	[1, 11]
Thyroxine-binding globulin	2.5	2.3	0.8	5.0 [a]	3.7	0	0.5	14.8	[37]
Ceruloplasmin	1.2	1.8		2.4	2.4	0.18		7.98	[38]
Haptoglobin	2.8	2.8		5.3	5.3	0.2		16.4	[39]
α_2-Macroglobulin	1.36	2.07		3.94	1.80	0.26		9.43	[40, 17]
Hemopexin	3.08	3.84		7.7	6.9	0.4		21.92	[41]
Transferrin	0.74	1.85		2.0	1.3			5.89	[42]
C1q	2.62	0.87	2.53	1.35 [a]	0.31	0.13		7.81	[43, 44]
J-Chain [mol] [b]	2	3		3—4	1	1			[45]
Secretory component	3.12	3.95		4.36	1.9	2.26		15.59	[46]

[a] Free base.
[b] The J chain is an additional chain in IgA and IgM.

Table 4. Contents of the sugar units as fractions of the total carbohydrate content.

	Hexoses [%]	Ac-hexos-amine [%]	Ac-neur-aminic acid [%]	Fucose [%]
α_1-Acid glycoprotein	35	35	29	1.8
α_1-Antitrypsin	41	29	28	1.6
Prothrombin	39	25	36	
α_1B-Glycoprotein	36	33	28	
Transcortin	38	33	23	5.7
Thyroxine-binding globulin	35	39	23	3.1 (Xylose)
α_1T-Glycoprotein	40	33	25	2.2
α_1-Antichymotrypsin	40	30	27	2.8
9.5S-α_1-Glycoprotein	43	29	27	0.8
α_1-Fetoprotein	33	29	38	
Gc-Globulin	48	48	0	4.8
Inter-α-trypsin inhibitor	37	38	24	1.2
Antithrombin III	46	31	23	
Ceruloplasmin	37	30	30	2.5
Zn-α_2-Glycoprotein	38	22	38	
α_2-HS-Glycoprotein	39	29	31	1.5
C1-Inactivator	31	26	38	1.1
Histidine-rich 3.8S-α_2-glycoprotein	45	31	24	0
Haptoglobin	34	32	32	1.2
α_2-Macroglobulin	36	42	19	2.8
	41.5	35	22	1.3
Serum cholinesterase	39	35	25	0.8
8S-α_3-Glycoprotein	35	34	29	1.3
Hemopexin	31.5	35	31	1.8
Transferrin	44	34	22	
Fibrinogen	39	36	25	0
Factor XIII	39	33	24.5	4.1
β_2-Glycoprotein I	41.5	33	24	1.6
C3-Activator / β_2-Glycoprotein II	39	31.5	26	3.5
β_2-Glycoprotein III	25	20	55	
IgG-Globulin	38	45	10	7
IgA-Globulin	43	31	24	2.7
IgM-Globulin	46	37	11	6
C1q	74	21	3.8	1.6
Secretory component	46	28	12	15

which constitute about 10—15% of the total serum proteins. In β-lipoprotein, with a peptide content of 26.5%, we found 1.4% of hexoses, 0.2% of neuraminic acid, and 0.45% of acetylhexosamine. α_1-Lipoprotein has a peptide content of 41% with 1.3% of hexoses, 0.1% of neuraminic acid, and 0.25% of acetylhexosamine. These results were confirmed in 1966[50]. Of the six apolipoproteins, *i.e.* the peptide chains that form the skeleton of the lipoproteins, apo-Ser and apo-Ala contain carbohydrates[51].

It is now possible to compare the analytical values for very many more glycoproteins than was formerly the case. An important contributory factor here has been the work carried out in our laboratories on highly purified glycoproteins isolated from side fractions of the industrial plasma fractionation.

Examination of the tables shows that the carbohydrate contents of the plasma proteins cover a wide range. Prealbumin contains only 0.4% of hexoses, whereas the α_1-acid glycoprotein has a total carbohydrate content of about 38%. (Recent gas-chromatographic analyses indicate that prealbumin contains no carbohydrates at all[52]; moreover, the detection of such small quantities of hexoses by the orcinol method used by us is problematic.) The α_1-acid glycoprotein is taken as a standard type for structural investigations on serum glycoproteins.

The relations of the sugars to one another also vary. For example, Gc-globulin contains no neuraminic acid. There is no fucose in the histidine-rich α_2-glycoprotein, in fibrinogen, or in β_2-glycoprotein III. No galactosamine can be detected in the α_1-acid glycoprotein.

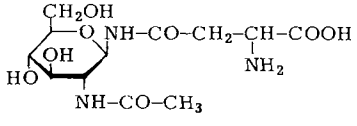
The galactose: mannose ratio (Table 3) is >1 in the carbohydrate-rich α_1-globulins, 1 in haptoglobin, and <1 in a number of other glycoproteins. The ratio total sugars: hexosamine is generally in the region of 2.9—3.4. The hexose: hexosamine ratio is 1 or slightly higher. The "secretory component" and C1q are exceptions here. C1q also has peculiarities in its amino acid composition[43].

The highest neuraminic acid values go together with a particularly high total carbohydrate content. This applies to the C1 inactivator and the α_1-acid glycoprotein. β_2-Glycoprotein III, with a total carbohydrate content of only 10%, has the highest relative content of neuraminic acid. Since the neuraminic acid residues carry a negative charge they give the glycoproteins a greater electrophoretic mobility. This is particularly noticeable in the case of the immunoglobulins (Tables 2 and 3).

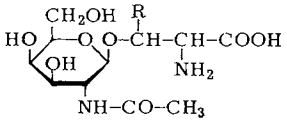
2.2. The Carbohydrate-Peptide Bond[11]

The carbohydrates are bonded to the peptide chains in the form of large oligosaccharide units. The molecular weights of these sugar complexes are 2370 in transferrin and 3170 in the α_1-acid glycoprotein. For investigations on the nature of the bond, the glycoproteins are treated either with pronase, a proteinase from *Streptomyces griseus*, or with a combination of pepsin, trypsin, chymotrypsin, or papain. The glycopeptides can be separated from the cleavage mixtures by fractionation. Excess amino acid residues are removed with pronase or carboxypeptidase.

The elucidation of the bonding is facilitated by the fact that the asparagine-carbohydrate bond is relatively stable to alkalis and acids. It is more stable to dilute acids than the glycoside linkages in the oligosaccharide complexes. It was therefore possible to isolate the compound *(1)* from a glycopeptide; in this compound the sugar complex



(1)

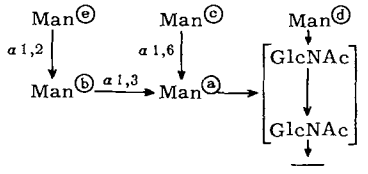


(2)

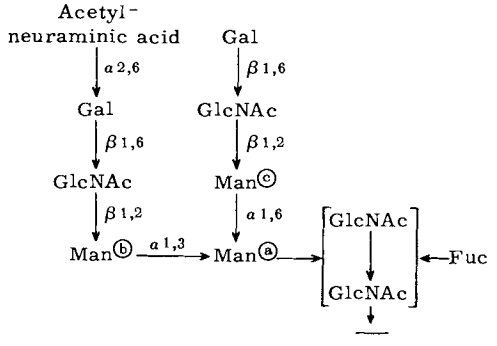
is bound *via* the reducing group of *N*-acetylglucosamine to the amide group of asparagine. This type of binding is characteristic of most plasma proteins. In addition to this *N*-acylglycosylamine linkage, the *O*-glycoside linkage as in *(2)* is also found[53]. In this case the sugars are bound *e.g. via* *N*-acetylgalactosamine to the hydroxyl group of threonine or serine. This linkage occurs together with the *N*-acylglycosylamine linkage in human IgA[54] and in rabbit IgG[55]. A Waldenström IgM was found to contain only the *N*-glycoside linkage[56].

2.3. Structure of the Oligosaccharide Units

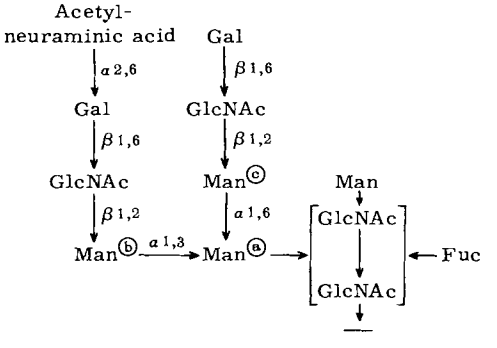
The sequence of the sugar units is determined by successive enzymatic degradation of the glycopeptides with glycosidases. Neuraminidase, β-galactosidase, α-mannosidase, and β-acetylglucosaminidase are used for this purpose[57].



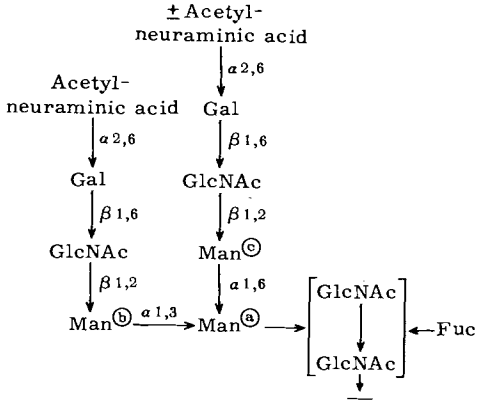
Glycopeptide I



Glycopeptide IV



Glycopeptide V



Glycopeptide VI

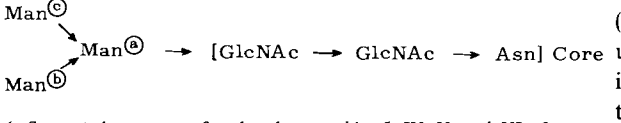


Fig. 1. Suggested structures for the glycopeptides I, IV, V, and VI of immunoglobulin M (IgM) after *Hickman et al.* [58]. The bonding asparagine residue counts as part of the core.

The enzymes also provide information on the type of linkage by which the sugar residues are joined. Further information on this point is obtained by periodate oxidation and by methylation of the glycopeptides with subsequent characterization of the alditol acetate derivatives of the methylated sugars by gas chromatography and mass spectrometry[58,59]. Alkaline hydrolysis followed by deamination with nitrous acid has recently also been recommended[60].

Investigations on the oligosaccharide units of IgM have shown that they are derived from two basic types: a simple type that consists only of *N*-acetylglucosamine and mannose and a complex type that also contains galactose, fucose, and neuraminic acid (Fig. 1). They evidently contain a common core. A fundamentally similar structure of the carbohydrate groups was also found earlier in the α_1-acid glycoprotein[1], fetuin, α_2-macroglobulin, transferrin[61], IgA[54], and IgG[62].

The sugar complexes are thus bonded to the peptide chain *via* *N*-acetylhexosamine in every case. In the α_1-acid glycoprotein, the carbohydrate group branches at the *N*-acetylglucosamine according to *Wagh*[63], while according to *Sato* it branches only at the mannose[1]. Mannose is also the branching point in transferrin[61] and in other immunoglobulins. The neuraminic acid (which is present as *N*-acetylneuraminic acid) and the fucose are terminal. Positional isomerism is therefore possible for these residues. The neuraminic acid is bonded to galactose. However, the α_1-acid glycoprotein also appears to contain one to three more difficultly removable neuraminic acid residues which are linked to *N*-acetylglucosamine[60].

Deviations from the normal structure of the sugar complexes have been observed for several proteins. A transferrin poor in neuraminic acid has been found in cerebrospinal fluid[7,64]. α_1-Acid glycoprotein poor in neuraminic acid has been found in the serum and urine of patients with Hodgkin's disease, psoriatic arthritis, and diabetes[65,66]. The explanation offered is that these patients with chronic diseases form glycoproteins in unusually large quantities over a long period, and that this causes their synthesis capacity to decrease. Variations of the carbohydrates has also been described in the case of fibrinogen[67,68]. Coagulation factor X from bovine plasma appears to occur in two forms; factor X-I has one to two neuraminic acid residues and one to two hexose residues less than factor X-II, though its coagulation activity is the same[69].

2.4. Localization of the Carbohydrates in the Peptide Chains

The exact localization of the carbohydrate complexes (denoted here by C1, C2, *etc.*) in the peptide chains is at present known only for IgM and IgG globulins and for the α_1-acid glycoprotein. In human IgM, each monomer (molecular weight 180000) contains ten oligosaccharide units[70], *i.e.* five for each μ chain (Fig. 2). C1 is situated in the Fd region, at about amino acid 170, and C2 in the hinge region near the disulfide bridge around position 230. C3, C4, and C5 are in the Fc region. C1, C2, and C3, which are situated in the interior of the molecule,

are of the complex type, whereas C4 and C5 consist only of hexosamine and mannose.

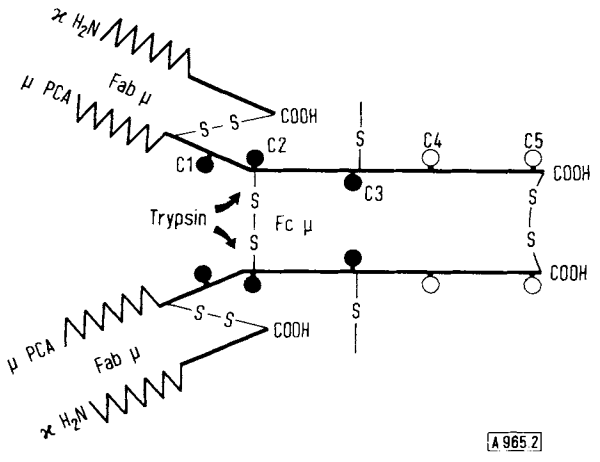


Fig. 2. Scheme of the polypeptide chain structure of a monomer unit of human IgM Ou with the positions of carbohydrate complexes C1—C5 (after [70]). PCA = 5-oxopyrrolidinecarbonyl.

These observations, which were made on the two Waldenström IgM globulins Ou and Di, have been confirmed for the IgM paraprotein Dau[71]. The carbohydrate compositions of the five oligosaccharide units of these three IgM globulins can be seen from Table 5. Apart from the mannose values in italics, the agreement is very good. It was particularly important in these investigations to ensure that the J chain was removed, since this also contains carbohydrates (see Table 3).

Table 5 also shows the microheterogeneity of the glycoproteins. Nearly all glycoproteins appear to contain the carbohydrate units in various stages of completion or with small modifications[2,58,72,73]. (It is not entirely correct to take the Waldenström globulins as an example for the demonstration of this microheterogeneity, since each paraprotein is unique; this is true of its amino acids, and possibly also of its carbohydrates.)

IgG contains only about one quarter of the carbohydrates (2.9%) present in IgM. In the case of rabbit IgG, these are present in three oligosaccharide units[55] (Fig. 3). C1 is situated in the Fd part of each of the two H chains and is detectable in about 15% of the molecules. C2 is situated unsymmetrically on only one H chain close to the disulfide bridge in about 80% of the molecules. C3 is again attached to both H chains in the Fc region (in position 67 reading from the carboxyl end) and appears to be present in all IgG molecules.

The fact that in addition to carbohydrate-poor IgG molecules there are also carbohydrate-richer molecules with several sugar units has also been reported in the case of human IgG[74]. Out of 76 IgG myeloma globulins, 29% had a higher carbohydrate content. In the carbohydrate-poor molecules, the carbohydrates are localized only in the Fc part. An example of this is the IgG1 globulin Eu, whose complete amino acid sequence is known and whose carbohydrate unit is attached to asparagine-297[75].

In molecules with a 2 to 2.5 fold increase in the carbohydrate content, the sugars also occur in the Fd part or in the L chains. In molecules with a 3 to 4-fold increase

Table 5. Carbohydrate composition of the glycopeptides of the IgM globulins Dau, Ou, and Di; values in residues per molecule (after [71]).

Dau	H chain [a]	C1	C2	C3	C4	C5	Total
Fucose	2	1	1				2
Mannose	17	3	*6–7*	2	*3*	*3–4*	17–19
Galactose	5	1	2	1			4
Glucosamine	10	2	3	2	1–2	2	10–11
Acetylneuraminic acid [b]	4						
Ou and Di	**H chain [a]**	**C1**	**C2**	**C3**	**C4**	**C5**	**Total**
Fucose	2.5	1	1	1			3
Mannose	15–17	2–3	*2–3*	3	5	*8–11*	20–25
Galactose	5–5.5	2	2	2			6
Glucosamine	12–13	3	3–5	*4–5*	2	2–3	14–18
Acetylneuraminic acid	4						

[a] H chain = heavy chain of immunoglobulin.
[b] Not determined because of lack of material.

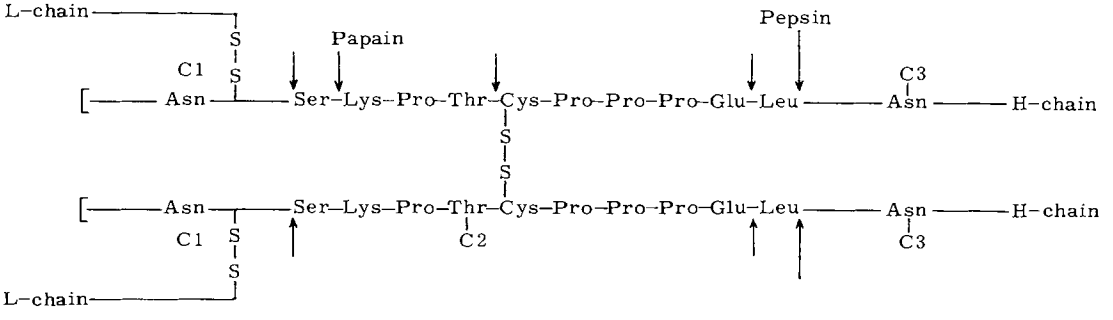


Fig. 3. Peptide chain structure of rabbit IgG with the carbohydrate units C1, C2, and C3 (after [55]).

in the sugar content, they are found in the Fc and Fd parts and in the L chains. The carbohydrate-rich IgG molecules also contain more acetylneuraminic acid. Their acetylneuraminic acid : fucose ratio is 0.44—0.98, compared with 0.18—0.27 in the carbohydrate-poor IgGs.

Because of this higher content of acetylneuraminic acid, the carbohydrate-rich IgG molecules migrate more rapidly in electrophoresis. We had already been able to isolate faster-migrating IgG globulins of this type from highly purified normal serum gamma globulins by preparative zone electrophoresis. They contained 0.47% of acetylneuraminic acid, whereas the slowest IgG fraction contained only 0.18% of acetylneuraminic acid[76].

Abel et al.[74] estimate that 91% of IgG molecules are carbohydrate-poor and 9% carbohydrate-rich. The carbohydrate content of 2.9% is an average value. The IgM also contains molecules with L-chain carbohydrates. Bence-Jones globulins can therefore also contain carbohydrates, depending on the paraprotein from which they are derived[77].

The α_1-acid glycoprotein is a one-chain protein containing about 210 amino acids and five oligosaccharide units, all of which are situated in the N-terminal third of the molecule and attached to asparagine (Fig. 4)[78]. For a number of other proteins (Table 6) only the number of sugar units per molecule is known. Human fibrinogen, with a carbohydrate content of 2.8%, has sugar units in the Bβ and γ chains. The A_α chain is free from carbohydrate[79].

PCA–Ile–Pro–Leu–Cys–Ala–Asn–Leu–Val–Pro–Val–Pro–
C1
Ile–Thr–Asn–Ala–Thr–Leu–Asp–Arg–Ile–Thr–Gly–Lys–
Ala–Tyr–Ile–Ala–Ser–Ala–Phe–Arg–Asn–Glu–Glu–Tyr–
C2
Asn–Lys–Ser–Val–Gln–Glu–Ile–Gln–Ala–Thr–Phe–Phe–
C3
Tyr–Phe–Thr–Pro–Asn–Lys–Thr–Glu–Asp–Thr–Ile–Phe–
Leu–Arg–Glu–Tyr–Gln–Thr–Arg–Gln–Asp–Gln–Cys–Ile–
C4 C5
Tyr–Asn–Thr–Thr–Tyr–Leu–Asn–Val–Gln–Arg–Glu–Asn–
Gly–Thr–Ile–Ser–Arg–Tyr–Thr–Ile–Ser–Arg–Tyr–Val–
Gly–Gly–Gln–Glu–His–Val–Ala–His–Leu–Leu–Ile–Leu–
Arg–Asp–Thr–Lys–Thr–Leu–Met–Leu–Ala–Phe–Asp–• • • •

Fig. 4. Section of the peptide chain of the α_1-acid glycoprotein with the five oligosaccharide units (after [78]).

Table 6. Oligosaccharide units in glycoproteins.

	Chains	Units/ molecule	Ref.
α_1-acid glycoprotein	1	5	[78]
Ceruloplasmin	1 (dimer)	6	[38]
α_2-Macroglobulin	10	31	[72]
Haptoglobin 2-1	4β	13	[80, 81]
Transferrin	1 (dimer)	2 identical	[42]
Fibrinogen	Bβ (dimer)	2?	[79]
	γ (dimer)	2	
IgG	$(L, H)_2$		
IgM	$(L, H)_{10}$	2 simple, 3 complex } × 10	

2.5. Influence of the Carbohydrates on the Physico-Chemical Behavior of the Glycoproteins

The high neuraminic acid content of the α_1-acid glycoprotein affects its physico-chemical behavior[82]. Comparative studies on the intrinsic viscosities, diffusion and frictional coefficients, and behavior in the ultracentrifuge of the native and the neuraminic acid-free glycoprotein indicate that the native molecule has a somewhat less regular shape. This shape could be explained by the assumption that all the neuraminic acid residues are localized in the N-terminal third of the peptide chain, and that this part of the molecule may therefore be more strongly hydrated than the other parts.

The high carbohydrate content also affects the determination of the molecular weight. In the gel filtration method with Sephadex G-75, for example, a molecular weight of 60000 is found for the α_1-acid glycoprotein (correct value: approx. 44000)[83]. When acrylamide gel electrophoresis in the presence of sodium dodecyl sulfate is used for the determination of the molecular weight, the values found depend on the degree of crosslinking of the gel[84]. This anomaly is attributed to weaker binding of the dodecyl sulfate by the oligosaccharide units than by the protein part.

Because of their strong hydration, the carbohydrate groups cause increased solubility of the glycoproteins. Thus the serum proteins that are richest in carbohydrate, *i.e.* C1 inactivator, α_1-acid glycoprotein, and hemopexin, belong to the seromucoid fraction. These proteins are not precipitated by perchloric acid and trichloroacetic acid, exhibit considerable heat resistance in solution, and require much greater quantities of precipitants for precipitation[85, 86].

A particularly interesting phenomenon is that of the freezing-point depressing glycoproteins of the Antarctic fish *Trematomus borchgrevinki*. These keep the blood from freezing even at −1.9 °C. There are essentially three glycoproteins involved, with molecular weights of 10500, 17000, and 21500. They are built up from Ala-Ala-Thr units. All the threonines are *O*-glycosidically linked to galactosyl-*N*-acetylgalactosamine. The activity is lost on oxidation of the hydroxyl groups of the sugar to carboxyl groups. At low concentrations (< 1%) these glycoproteins are as effective as sodium chloride. They thus cause a freezing point depression some 100 to 1000 times as great as that expected from their molecular weight[87, 88].

In ceruloplasmin, chemical changes influence the crystalline form. The native protein forms tetragonal prisms, while the neuraminic acid-free protein forms hexagonal prisms[89].

3. Significance of the Carbohydrate Component

The glycoproteins are responsible for important biological functions. They act as transport proteins, inhibitors,

enzymes, hormones, coagulation factors, complement factors, and antibodies. One might ask whether the carbohydrate component has anything to do with their function. This question is not easy to answer, as we still know too little. Some information is available only in connection with the significance of neuraminic acid. This terminal sugar can be relatively easily split off by neuraminidase[90]. A highly purified enzyme from *Vibrio cholera*, which is free from proteases, is available for investigations of this type.

3.1. Role of Neuraminic acid

The influence of treatment with neuraminidase on the biological activity of important glycoproteins is shown in Table 7. Some, including the hormones, are inactivated. The proteinase and complement inhibitors are not affected. The antibodies also suffer no loss of activity. The transport proteins can still bind their ligands and transport them. For example, neuraminic acid-free transferrin can still supply iron to the reticulocytes[91,92]. The bonding of cortisone to transcortin[93] or of progesterone to the α_1-acid glycoprotein[94] is also still possible.

Table 7. Influence of neuraminidase treatment on the biological activity of some glycoproteins.

Inactivation	No loss of activity	
Choriongonadotropin (HCG)	Cholinesterase	α_1-Antitrypsin
Follicle-stimulating hormone (FSH)	Thrombin	Antithrombin III
Erythropoetin	Hageman factor	Inter-α-inhibitor
MN substance	Transcortin	α_2-Macroglobulin
Migration inhibiting factor (MIF)	Thyroxine-binding globulin	C1-Inactivator
	Haptoglobin	
	Ceruloplasmin [a]	Antibodies
	Transferrin	
Fibrinogen		
Prothrombin		

[a] Binding of copper and oxidase activity.

Neuraminic acid-free ceruloplasmin injected into rabbits is eliminated from the circulation within a few minutes, and is then found in the liver parenchyma cells. These cells evidently have a special affinity for the galactose residues. On removal of the new terminal galactose with β-galactosidase, one again finds half-lives equivalent to those of native ceruloplasmin[95-97].

Removal of neuraminic acid from fibrinogen leads to a change in the structure of the fibrin clot[98,99], and neuraminic acid-free prothrombin, as we found earlier, is converted more rapidly into thrombin in concentrated citrate solution[100].

A phenomenon that is also closely related to the neuraminic acid content is the hemagglutination inhibition caused by influenza virus. Table 8 shows a number of serum glycoproteins arranged in order of their inhibitor activity towards the strain B/Maryland[101]. The inhibitor activity does not run parallel to the neuraminic acid content, since the α_1-acid glycoprotein, with 12% of neuraminic acid, is only a weak inhibitor in comparison with the uromucoid of *Tamm* and *Horsfall*, which contains only 7% of neuraminic acid. The inhibitor action increases after polymerization of the α_1-acid glycoprotein. A sufficiently high molecular weight is therefore essential. The fact that the glycoproteins exhibit different inhibitor effects against other strains of virus indicates that a special steric arrangement of the receptors is necessary. The terminal neuraminic acid residues of the glycoproteins occupy the neuraminidase receptors of the virus particles, so that these can no longer react with the erythrocytes[1,101].

3.2. Participation of Other Sugar Units

We have evidence for two other proteins that the carbohydrates are directly responsible for their activity. The complement component C9, which is responsible for the final phase of the complement reaction, forms a chelate with iron[102]. In its biological activity, it can be replaced by *o*-phenanthroline. In this case, the iron is bonded by the carbohydrates, since C9 is inactivated on oxidation with potassium metaperiodate. The ability of carbohydrate-rich glycoproteins to bind iron is demonstrated particularly impressively by gastroferrin[103]. This iron-binding glycoprotein of the gastric mucosa, with a molecular weight of about 260000, has a carbohydrate content of about

Table 8. Serum glycoproteins as inhibitors of hemagglutination due to influenza virus (strain B/Md) (after [101]).

	Inhibitor activity	Mol.-wt.	Neuraminic acid [%]	Neuraminic acid [mol/mol]
Blood group substance MM	100	12000000	11.5	4466
Uromucoid [a]	400	7000000	7.0	1586
IgM-Globulin	25	900000	1.8	405
Haptoglobin 1-1	25	85000	5.2	14
Fetuin (bovine)	12.5	45000	4.5	9
Hemopexin	10	80000	5.0	13
α_1X-Glycoprotein	6.25	60000	7.0	14
α_2-Macroglobulin	5	820000	1.8	48
β_2-Glycoprotein 1	1.67	40000	4.5	6
α_1-Acid glycoprotein	0.80	44000	12.1	17
Ceruloplasmin	0.80	160000	2.4	12
Zn-α_2-Glycoprotein	0.80	41000	4.7	6
IgA-Globulin	0.80	160000	1.3	11
α_1-Antitrypsin	0.53	54000	3.6	6
α_1-T-Glycoprotein	0.40	60000	7.0	7

[a] Of *Tamm* and *Horsfall*.

85%. It is able to bind 6% of its own weight of iron. Neuraminic acid plays no part here.

A second example is the relatively obscure "colony stimulating factor" for granulocytes and macrophages, which is also inactivated on oxidation of the carbohydrates[104].

3.3. Carbohydrates as Inhibitors of Biological Reactions

The carbohydrates cover considerable parts of the surface of the glycoproteins and can thus inhibit the action of proteolytic enzymes. For example, native α_1-acid glycoprotein is split only with difficulty by trypsin and papain[105]. Ceruloplasmin is also known to have a certain resistance to papain[106]. Faster-migrating IgG globulins which have a higher carbohydrate content are similarly characterized by relatively high stability to hydrolysis[107]. The exocrine IgA, which exerts its protective function *e. g.* in the intestinal mucosa as a copro-antibody, should have a very high resistance to bacterial and digestive enzymes because of its carbohydrate content of 12%[108,109]. On the other hand IgD, with roughly the same carbohydrate content, is extremely readily attacked by proteolytic enzymes. Its carbohydrates appear to be situated in the Fd and Fc parts[110]. They must be so far apart that the hinge region is readily accessible for cleavage.

The α_1-acid glycoprotein can bind vitamin B_{12}, but has only a relatively low binding capacity in the native state. On removal of the neuraminic acid, the binding of vitamin B_{12} increases by a factor of 4[111]. The immunogenicity of the α_1-acid glycoprotein should also be increased by removal of the neuraminic acid. This procedure is recommended for the preparation of antiserums against this protein[112].

The removal of neuraminic acid has recently become interesting in tumor immunology. For example, tumor cells are treated with neuraminidase and reinjected into the patient with or without BCG[113,114]. The immune cells should now recognize the tumor antigens and destroy the tumor with the aid of antibodies, complement, and cellular immunity.

The fact that carbohydrates, and particularly neuraminic acid, hinder the development of humoral or cellular immunity is also of interest for transplantation immunology. In addition to immunosuppressive drugs, serum proteins are also able to suppress sensitization[115]. The best known and the most extensively discussed is *Mowbray*'s α-globulin[116]. This protein was able to inhibit antibody formation and the rejection of transplants. The experiments were difficult to reproduce, and it was finally concluded that the immunosuppressive action was due to ribonuclease activity. *Schmid et al.*[117] recently succeeded in isolating a peptide having a molecular weight of 4000—6000, which is practically free from carbohydrate, from *Cohn*'s fraction IV. This peptide can prevent the phytagglutinin-induced proliferation of lymphocytes and inhibit the formation of plaque-forming cells in mice immunized against sheep erythrocytes.

These substances do not appear to be identical with the chalones. These are substances that inhibit cell proliferation in certain tissues, *i. e.* inhibitors of mitosis. They are formed by the cells of this tissue, *e. g.* by lymphocytes, granulocytes, or fibroblasts, and are also important in transplantation and tumor immunology[118–120]. They can be isolated from diploid human fibroblasts, bovine spleen, or calf thymus. The molecular weights are between 30000 and 50000. The chalone from calf thymus is an acidic α-glycoprotein, and it seems reasonable to ask whether it is related to the α_1-acid glycoprotein.

3.4. Biological Properties in which Carbohydrates Play No Part

There are regions on the Fc part of the immunoglobulins that are important to placenta permeability, complement binding, phagocytosis, and species-specificity. Carbohydrates had been held responsible in particular for the first of these properties[121]. As has been shown by comparison of native mouse immunoglobulin with mouse immunoglobulins that had been treated with specific glycosidases, however, the sugars are not necessary for the placenta permeability[122].

The sugars also appear to be of no importance to the complement binding of the IgG globulins[123]. Isolated IgG glycopeptides did not affect complement binding, and twelve IgG myeloma globulins having different carbohydrate contents showed no dependence of the complement binding on the sugar content[124]. In phagocytosis experiments with numerous plasma proteins, we were unable to find any evidence of dependence on the sugars[125]. IgM, with a carbohydrate content of about 10%, stimulated phagocytosis effectively, but the carbohydrate-free C-reactive protein caused practically the same phagocytosis.

The species-specificity of the immunoglobulins also does not appear to involve the carbohydrates. The latter are not immunogenic[126]. A possible reason for this is that there are only a few basic types of glycoprotein-oligosaccharide units (Fig. 1) and that these have remained practically the same in the course of evolution. They are of widespread occurrence, and the body therefore does not react to them as to foreign substances.

This abundance of facts leads us to wonder about the true significance of the carbohydrates. Is there a single underlying principle common to all these phenomena, or are the sugars only there by accident, a relic of the dim past and of evolution?

3.5. Evolution of the Glycoproteins

Analyses of the amino acid sequences of a number of proteins have confirmed *Darwin*'s views. The major stages of evolution can be followed from the changes in the sequence of cytochrome c[127]. This protein, which plays a part in biological oxidation in the cells, has changed least in the course of evolution. The fine points of our family tree, particularly of the latest phases, can be seen from hemoglobin[128]. However, these two proteins contain no carbohydrate.

Because of their importance in prophylaxis and therapy, the immunoglobulins are the most extensively studied of the serum glycoproteins[129,130]. According to *Porter* and *Edelman*, who received the Nobel prize for this work in 1972[131], they consist of two light (L) and two heavy (H) peptide chains. The L and H chains are thought to be derived from an ur-gene, which codes only half of the L chain, and from which the present-day immunoglobulin genes have developed by gene duplication and hypermutation[132-135]. The chains of IgM, *i.e.* the μ chains, are probably biogenetically the oldest of the H chains.

In addition to the amino acid sequence, the carbohydrate composition also provides important information on the evolution of the immunoglobulins[136,137]. Thus the carbohydrate contents of the high molecular weight antibodies (IgM), whose H chain has a molecular weight of about 70000, have remained practically unchanged (Table 9). They also agree with the 7S-IgM antibodies that occur in some species, with which they are antigenically identical. The only exception is chicken IgM globulin, which has a lower carbohydrate content.

segment of this type containing carbohydrate is missing, as in the turtle, the carbohydrate content of the H chain is very low. On the other hand, if a chain segment that is poor in carbohydrate is missing because of divergent gene duplication, as could be the case in the African lungfish, the carbohydrate content of the H chains may be higher than for the H chains with three constant regions.

The molecular weight of the H chain of the LMW antibody in chickens is 66000. One might ask whether the increased carbohydrate content in comparison with that of human IgG could be due to an additional constant chain segment containing carbohydrate. There may be a relationship between this divergent structure and the changes in the conformation of chicken antibodies in salt solutions of various concentrations, which are thought to be responsible for the special precipitation behavior of chicken antibodies in agar gel[139]. It is well known that chicken antibodies require an NaCl content of 8% for the formation of immune precipitates.

Mannose, galactose, glucosamine, and acetylneuraminic acid have been found in the immunoglobulins of all species

Table 9. Carbohydrate composition of immunoglobulins of various species. AR = complete antigen relationship between HMW and LMW.

Class	Species [a]	Hexose [%]	Hexosamine [%]	Fucose [%]	Acetyl-neuraminic acid [%]	Total carbohydrate content [%]	AR
Cartilaginous fishes	Horned shark						
	Heterodontus francisci						
	HMW 70000	4.1	3.4	0.45	1.4	9.3	+
	LMW 70000	5.5	4.4	0.5	1.5	11.9	
Bony fishes	African lungfish						
	Protopterus aethiopicus						
	LMW 38000	2.4	2.1	0.45	0.03	5.0	–
	Paddle fish						
	Polyodon spathula						
	HMW 70000	5.9	3.3	1.1	0.5	9.0	+
	LMW 70000	4.1	2.9	1.0	0.1	8.1	
	Bowfin						
	Amia calva						
	HMW 70000	5.9	3.3	0.7	0.8	10.7	+
	LMW 52000	4.8	2.6	0.6	1.1	9.1	
Reptiles	Turtle						
	Chelydra serpentina						
	LMW 38000	0.2	0.05	0.4	0.2	0.8	–
Birds	Chicken						
	Gallus domesticus						
	HMW 70000	3.2	2.9	0.5	0.6	7.2	–
	LMW 66000	2.0	1.25	0.45	0.4	4.1	
Mammals	Man						
	Homo sapiens						
	HMW (IgM) 70000	5.6	4.2	1.0	1.3	12.1	–
	LMW (IgG) 50000	1.0	0.9	0.3	0.2	2.4	

[a] The abbreviations HMW (high molecular weight) and LMW (low molecular weight) refer to molecular weights of IgM ~ 900000 and IgG ~ 150000 resp. for the native antibodies.

The H chains of IgG globulin, the γ chains, with molecular weights of about 50000, have nothing to do with the μ chain as far as common antigen determinants are concerned. As was shown in Table 2, they have a total carbohydrate content of less than 3% in man. The γ chains normally consist of a variable part (V) and three constant parts (C_1, C_2, and C_3), whose region covers about 110 amino acids with a molecular weight of about 12500[138]. If one of these constant regions is missing, as in the H chain of the turtle or of the African lungfish, the molecular weight of these shortened H chains is only about 38000.

In bovine IgG, the complex oligosaccharide unit C3 is localized in the C_3 region of the H chain. If a chain

of vertebrates investigated. The mannose:galactose ratio was greater than 1 in mammals and birds, and was of the order of 1 in animals below the birds. Fucose was absent in two of the species investigated[140]. The carbohydrate composition of the transferrins also differs considerably according to the species[141,142]. The differences are explained by the assumption that the proteins should contain different numbers of heteropolysaccharide units, *i.e.* one in monkey (macaque), chicken, and bovine transferrins, two in human, horse, and rabbit transferrins, and four in pig transferrin.

The relationship recently found by amino acid sequence analyses between the immunoglobulins and the α_1-acid

glycoprotein is particularly interesting in connection with the biogenetics of glycoproteins[143]. As can be seen from Fig. 5, the peptide chain of the α_1-acid glycoprotein contains two partial sequence duplications. Region B is homologous with the carboxyl end of segment A. Region D is homologous with region C. The amino-terminal segment

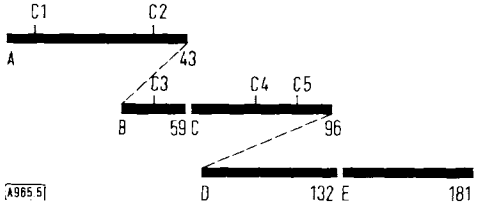


Fig. 5. Structure of the α_1-acid glycoprotein (cf. Fig. 4). To illustrate the homologous regions, the chain has been divided into regions A to E (after [143]).

A consisting of 43 amino acids is homologous with the amino-terminal end of the L chain (κ type) of IgG globulin. The 22 amino acids at the carboxyl end of region D exhibit a very high degree of homology with the α chain of haptoglobin[144]. Sequence E is homologous with a constant region of the H chain of rabbit IgG[*].

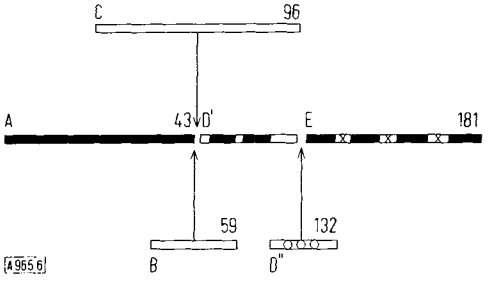


Fig. 6. Schematic representation of the "reduced" amino acid sequence of the α_1-acid glycoprotein. The regions B and C with sequence duplication and the haptoglobin sequence D are removed. The peptide chain then consists only of A, which corresponds to the variable region of the L chain of IgG, E, which resembles the constant region of the H chain of IgG, and a part of region D. It includes about 110 amino acids and is thus the hypothetic ur-immunoglobulin (after [143]).

If the segments with sequence duplication and the haptoglobin region are omitted, as shown in Fig. 6, one obtains a "reduced" peptide chain, which corresponds to the hypothetical ur-immunoglobulin. It is tempting to think that the α_1-acid glycoprotein arose from this.

In view of the genetic relationship between these two proteins, one may ask whether the α_1-acid glycoprotein still has any functional connection with immune defense, particularly since its content in the serum is greatly increased in all inflammatory processes, and how the sugars are incorporated into the peptide chain, *i. e.* how the glycoproteins are formed.

3.6. Synthesis of the Glycoproteins

There are essentially two sites for the synthesis of serum glycoproteins, *i. e.* the liver and the lymphoid tissue. Exceptions are the fibrin-stabilizing factor, which comes from the platelets, and a number of glycoprotein hormones, which come from the pituitary and the placenta. Most glycoproteins are synthesized exclusively in the liver[145–147] (Table 10). Transferrin appears to be formed in the liver and in lymphocytes. The immunoglobulins come from plasma cells, which are derived from B-lymphocytes. The plasma cells responsible for the formation of the secretory IgA can produce the protein in mammary glands, bronchi, intestinal mucosa, *etc.* It is possible that other glycoproteins are formed in the lymphocytes.

Table 10. Site of synthesis of glycoproteins of human plasma.

Glycoprotein	Synthesis site
α_1-Fetoprotein	Liver
α_1-Acid glycoprotein	Liver
Vitamin-B_{12}-binding protein TC I	Leukocytes
α_1-Antitrypsin	Liver
Prothrombin	Liver
Gc-Globulin	Liver
Haptoglobin	Liver
Antithrombin III	Liver
Ceruloplasmin	Liver
C I-Inactivator	Liver
Cholinesterase	Liver
α_2-Macroglobulin	Liver
Transferrin	Liver, lymphatic tissue spleen, mammary glands, lymphocytes, macrophages
C4	Liver
Hemopexin	Liver
β_2-Glycoprotein I	Liver
Fibrinogen	Liver
Factor XIII	Liver
Fibrin-stabilizing factor	Thrombocytes
Immunoglobulins	Lymphatic tissue: lymph nodes, spleen, mammary glands, plasma cells

The glycoprotein synthesis could proceed in three ways[53, 73]:

1. Protein and carbohydrate groups could be synthesized separately and combined at the site of formation of the peptide chain, *i. e.* the ribosomes.

2. The incorporation of the carbohydrate groups could occur after the peptide chain has left the ribosome and while it is in the endoplasmic reticulum.

3. A combination of the above two possibilities would also be conceivable, part of the carbohydrates being incorporated in the ribosome phase and the remainder attached later. Successive incorporation according to possibility 3 appears to be valid for the synthesis of the serum glycoproteins in the liver and lymphocytes. It has been shown with radioactively labeled leucine and ^{14}C-monosaccharides that the L chain of an IgG myeloma globulin is synthesized in about 30—40 seconds in mice[148–150]. The entire peptide component of the IgG molecule is formed in about 90 seconds. The antibodies found in the ribosome fraction are practically free from carbohydrate and only glucosamine can be detected. The antibodies now migrate to the periphery of the cell. On the way there through the channels of the endoplasmic reticulum, further monosaccharides are attached in steps by several glycosyl transferases, which are localized along the membranes of the

[*] The data in Fig. 4 do not entirely agree with those in Figs. 5 and 6. Fig. 4 is based on a peptide chain of about 210 residues and Figs. 5 and 6 on a chain of 181 residues. However, this has no effect, in principle, on the information deduced from Figs. 5 and 6.

rough and smooth endoplasmic reticulum and in the Golgi apparatus. The terminal fucose and acetylneuraminic acid residues are incorporated last. It takes a total of about 20 to 30 minutes for complete antibody molecules to appear outside the cell.

If the incorporation of monosaccharides is inhibited[151] by addition of 2-deoxy-D-glucose[152], the new antibody molecules no longer migrate to the periphery. They remain in the membranes containing ribosomes, and cannot pass into the rough endoplasmic reticulum or from there to the smooth membranes. The sugars do not appear to be important for the transport of the glycoproteins from the smooth endoplasmic reticulum or the Golgi apparatus out of the cell.

The synthesis of the oligosaccharide units is not controlled by a ribonucleic acid code as in the case of the peptide chain, but depends on the presence of the appropriate glycosyl transferases in the tissue in which the synthesis takes place. The presence or absence of these enzymes is naturally determined genetically. In the synthesis of ovotransferrin (conalbumin), which is identical immunologically and in its amino acid structure with chicken serum transferrin, but has a different carbohydrate composition (it contains only glucosamine and mannose), the enzymes required for the incorporation of further sugar residues were evidently absent[153]. Since the incorporation into the peptide chain is not coded by RNA, but must nevertheless be genetically controlled, it was assumed that the signal for the action of the glycosyl transferases is fixed in the amino acid sequence. Wherever Asn-X-Thr or Asn-X-Ser (where X can be any amino acid) occurs in the amino acid sequence hexosamine is to be attached to asparagine[2, 3, 154]. The amino acid X is thought to determine the type of oligosaccharide unit. One objection to this hypothesis is that the ribonucleases A and B have the same amino acid sequence, but one contains sugars and the other does not. As was mentioned in the case of chicken transferrins, however, the occurrence and nature of the glycosyl transferases also play a part, and there must be no inhibitors present for the incorporation of the sugars. This explains the occurrence of the sugars in the glycoproteins but the question of their true significance has not yet been answered.

3.7. Function of the Carbohydrates in Glycoproteins

According to *Eylar*'s hypothesis[155], the significance of the sugars is that they allow the proteins formed in the cells to pass out through the cell membrane into the extracellular space. They are thus a sort of chemical pass. *Eylar*'s view appeared to be confirmed by the findings of *Melchers* and *Knopf*[148, 150] (see Section 3.6). However, there are also arguments against this view. For example, serum albumin, which constitutes the major part of the plasma proteins, is synthesized in cells and can pass through their membrane, though it contains no carbohydrates. The anterior lobe of the pituitary gland secretes hormones; three of these, *i.e.* LH, FSH, and TSH, are glycoproteins, while the other three, *i.e.* growth hormone, ACTH, and prolactin, are not. The more recent work of *Esterly*[151] and of *Melchers*[152] also throw doubt on the hypothesis. The many phenomena described agree more closely with the view of *Winterburn* and *Phelps*[156, 157]. According to this view, the sugars are receptors in a recognition process. Examples of positive recognition would be:

1. hormones that find their target cell *via* neuraminic acid residues, such as chorionic gonadotropin and FSH, and which are inactivated when the neuraminic acid is removed;
2. the rapid catabolism of neuraminic acid-free ceruloplasmin. As long as the neuraminic acid was terminal, the liver parenchyma cells did not recognize the protein. The galactose residues exposed on removal of the neuraminic acid, on the other hand, were immediately recognized, possibly by sialyl transferases of the cell membrane, and the asialo-ceruloplasmin disappeared from the blood stream in a very short time;
3. the hemagglutination by influenza viruses.

Negative recognition would be *e.g.* the masking of antigen determinants or the covering of large areas of the molecular surface. These are the phenomena mentioned in Section 3.3 that are important at present in tumor and transplantation immunology. In view of the topicality of these modern lines of medical investigation, it should be worthwhile to try to discover the significance of the glycoproteins.

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Photoelectron Spectra of Nonmetal Compounds and Their Interpretation by MO Models[1]

By Hans Bock and Brian G. Ramsey[*]

Dedicated to Professor Karl Winnacker on his 70th Birthday

The results of (low energy) photoelectron spectroscopy render possible a better appreciation of the "Nature of the Chemical Bond". The application of this new experimental method is demonstrated utilizing representative compounds of the nonmetal elements, and a close symbiosis delineated with molecular orbital models. In particular, general consequences are discussed concerning electron deficiency, σ- and π-interactions, electron pair delocalization, and substituent effects or geometric perturbations. Photoelectron spectroscopic ionization energies permit evaluation of parameters for specified molecular groups, allow correlation with numerous other experimental data, and are didactically valuable in the teaching of general chemistry.

Had Sisyphus not been king of Corinth, but a natural scientist, he would probably have been bound to the task of preparing a survey of a rapidly developing topic.

1. On the Interpretation of Photoelectron (PE) Spectra

The well known photoionization process of a neutral molecule M to its radical cation $\dot{M}^{\oplus}$,

$$M + h\nu \rightarrow \dot{M}^{\oplus} + e^{\ominus} \quad (1)$$

in which the photon energy $h\nu$ in excess of the ionization energy $IE_n(M)$ appears as the kinetic energy of the ejected electron,

$$h\nu = IE_n(M) + E_{kin}(e^{\ominus}) \quad (2)$$

is the basis of photoelectron (PE) spectroscopy. If one chooses—as was proposed by *Turner* and co-workers[2a]—a helium(I) discharge lamp, for which $h\nu = 21.21\,eV$[**], as a monochromatic photon source and counts the emitted electrons (counts per second) of given kinetic energy, this allows (eq. 3) all vertical[**] ionization energies to be observed up to 21.21 eV:

$$IE_n(M) = 21.21\,eV - E_{kin}(e^{\ominus}) \quad (3)$$

These ionization energies correspond to energy differences, ΔE_G, between the ground state of a molecule and the different radical cation states and can be correlated—within the restriction of unchanged geometry and other assumptions—with calculated SCF orbital energies, ε_j^{SCF}, *via* use of Koopmans' theorem[2b,3] (Fig. 1).

$$(\Delta E_G =)\ IE_n(M) = -\varepsilon_j^{SCF} \quad (4)$$

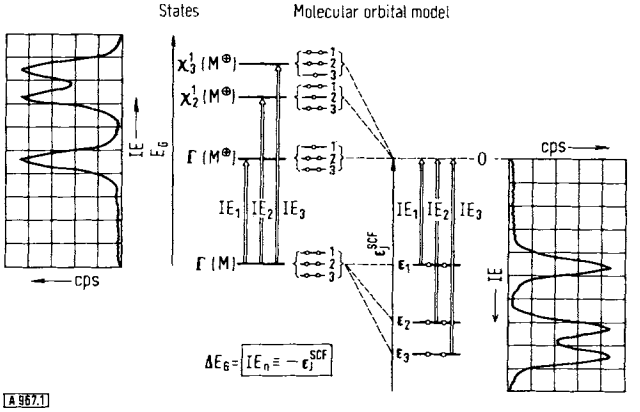

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Fig. 1. Koopmans' theorem: comparison of the measurable energy differences, $\Delta E_G = IE_n(M)$, between the molecular ground state $\Gamma(M)$ and the ground state $\Gamma(M^{\oplus})$ or excited states $\chi_n^m(M^{\oplus})$ of its radical cation with calculated SCF orbital energies, ε_j^{SCF}, (referred to the zero energy level of the removed electron) [***].

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[**] The reader will find in the reviews [2] a general description of the construction and operation of photoelectron spectrometers as well as a survey of different energy sources. The observed ionization potentials are independent of the energy of the photon source. A "vertical" ionization may be described as an electron ejection process which is so fast that the nuclear coordinates of the molecular framework remain unchanged.

[***] In contrast to simple MO methods, as for example the Hückel approximation probably known to the reader, SCF calculations are carried out by an iteration process by which a part of the electron-electron repulsion can be accounted for. It is also pointed out that in the transition from the state diagram to the molecular orbital model in Figure 1, the states are represented in a simplified manner by a single configuration. However, a complete description of the radical cation states χ_n^m is possible only on inclusion of configuration interaction.
In addition it should also be mentioned that an infinite number of sets of equivalent wave functions can be constructed from occupied SCF orbitals. They all permit calculation of the total energy of a molecule. From these sets, Koopmans' theorem selects only the set of canonical SCF orbitals [3a].

Generally, the vertical excitation ends in an additionally vibrationally excited state of the radical cation $M^{\oplus}$. Different possibilities are set forth in Figure 2 for the simplest example of a diatomic molecule AB.

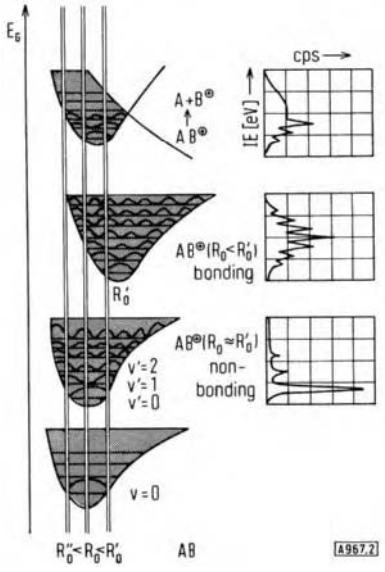


Fig. 2. Vertical [*] transitions between the vibrational ground state, $v=0$, of a diatomic neutral molecule AB and vibrational levels in different types of radical cation states $AB^{\oplus}$.

The minima of the potential energy curves (Fig. 2) represent the equilibrium bond distances R_0. These do not change significantly ($R_0 \approx R'_0$) if a "nonbonding" electron is ionized, and the vibrational frequencies remain approximately comparable ($v \approx v'$). Further, as one may gather from the overlap of the illustrated vibrational functions v and v', the transition from $v = 0$ to $v' = 0$ is the most intense, and the PE band consists of a sharp peak followed by peaks of greatly reduced intensity (Fig. 2). Normally in the ground state only $v=0$ is significantly populated. By contrast, on ionization of a bonding electron, the equilibrium bond distance increases ($R_0 < R'_0$), and the vibrational frequency decreases sharply ($v > v'$). At the same time a transition from $v=0$ to $v'>0$ is more probable and this results in a broad PE band, which may exhibit a vibrational fine structure as shown in Figure 2. From among other possible cases[2b], mention should be made of the predissociation $AB^{\oplus} \rightarrow A + B^{\oplus}$ which leads to a loss of band fine structure with increasing ionization energy (Fig. 2).

In addition to that from vibrational fine structure of PE bands, other information can be gathered from the spectrum about the radical cation state concerned. Thus, the splitting of certain PE bands through spin-orbit coupling of heavy atoms (Section 4.3) or through a Jahn-Teller distortion in degenerate radical cation states (*e. g.* allene *(8)*), often permits inferences about the nature of the electron removed by ionization. On the other hand, the intensity ratios of PE bands are not always simple to interpret[2b], and hence should only be used with caution as arguments for spectral assignments.

The assignment of PE spectra exclusively on the basis of spectroscopic data will be demonstrated with hydrogen bromide as an example. HBr contains eight valence electrons in the ground state. Of these, according to a useful rule of thumb, those with preponderant "$4s_{Br}$-character" should exhibit an ionization energy outside of the He(I) photon range of measurement, *i.e.* greater than 21.21 eV. The rest of the electrons are allocated to the two electron pairs n_{Br} and the σ_{HBr} bond.

The He(I) PE spectrum of hydrogen bromide[2a, 4] shows three bands in an approximate intensity ratio of 1 : 1 : 1 (Fig. 3). An unequivocal spectroscopic assignment succeeds

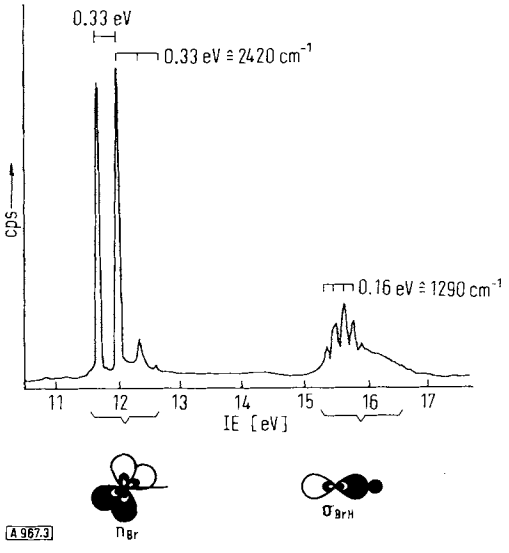


Fig. 3. He(I) PE spectrum of hydrogen bromide [2a, 4] with spectroscopic band assignments.

on the basis of: the vibrational fine structures (HBr: $2560\,cm^{-1}$; $HBr^{\oplus}$ $2420\,cm^{-1} \Rightarrow$non-bonding and $1290\,cm^{-1} \Rightarrow$bonding), the spin-orbit coupling of the bromide lone pair electron ($\Delta IE = 0.33$ eV), the wider band shape with increased bond participation, as well as the predissociative structure loss of the 15.6 eV band on the higher ionization energy side[2a] (compare Fig. 2).

In the case of molecules such as HBr, whose PE spectra allow spectroscopic assignment and which have an easily understood bonding system, one can act with Koopmans' theorem "as if orbital energies can be read directly from PE spectra". For the interpretation of the PE spectra of more complicated polyatomic molecules, one generally proceeds in a reverse manner, and the assignment will begin with qualitative, or where necessary, with the most rigorously calculable molecular orbital (MO) model. The comparison of chemically related compounds on the basis of perturbation arguments offers important aids to assignments. These combined methods will be illustrated here for the specific example of diborane[5].

Diborane, B_2H_6, contains twelve valence electrons, which in the ground state occupy pairwise six bonding molecular orbitals, and is isosteric with diprotonated ethylene $C_2H_6^{2\oplus}$. Hence, as a starting point, we selected the isoelectronic ethylene, whose six bonding molecular orbitals, as Figure 4 illustrates, may be constructed qualitatively according to the following approximate but reliable rules:

1) The energy sequence of the starting atomic orbitals is $C_{2p} > H_{1s} \gg C_{2s}$.

[*] See footnote [**] on p. 734.

2) The constructed symmetry-adapted linear combinations are ordered, each according to increasing number of nodal planes.

3) Orbitals of the same symmetry type mix and split apart, the magnitude of the splitting being directly proportional to the overlap of the orbitals and inversely proportional to their energy gap.

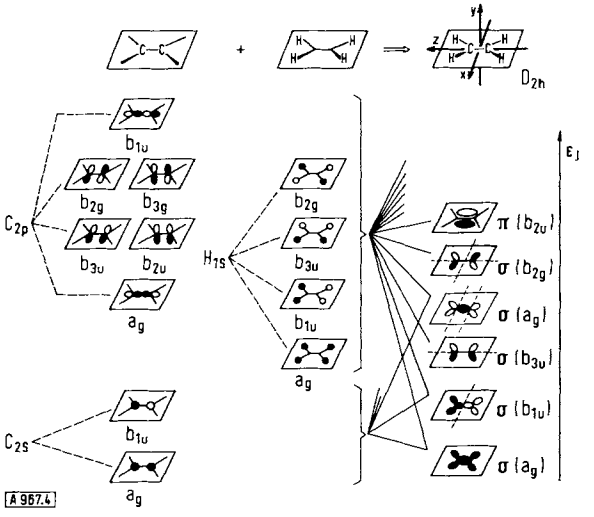


Fig. 4. Construction of qualitative symmetry-adapted linear combinations of atomic orbitals for ethylene.

An "unmixed" π MO and five σ MOs with differing CH and CC contributions result. Their energy sequence, estimated from the position of the starting orbitals as well as the increasing number and pattern of nodes, is confirmed through SCF "*ab initio*" calculations[5] (cf. Fig. 5), and is also in accord with the observable vibrational fine structure of the ethylene radical cation states in the PE spectrum[5]. The transition to diborane is made with two appropriate perturbation arguments: 1) $C_2H_4 \rightarrow B_2H_4^{2\ominus}$ (hypothetical), whereby, corresponding to the decrease in effective nuclear charge of boron as compared to carbon, a raising of all MOs is to be expected; and 2) diprotonation $B_2H_4^{2\ominus} \xrightarrow{2H^{\oplus}} B_2H_6$, in which the two additional positive hydrogen nuclei potentials, perpendicular to the σ molecular plane, should lower primarily the molecular orbital $1b_{2u}$. These plausible arguments are justified, both through the results of "*ab initio*" calculations and by the comparison of the PE spectra and their vibrational fine structure for ethylene and diborane[5] (Fig. 5).

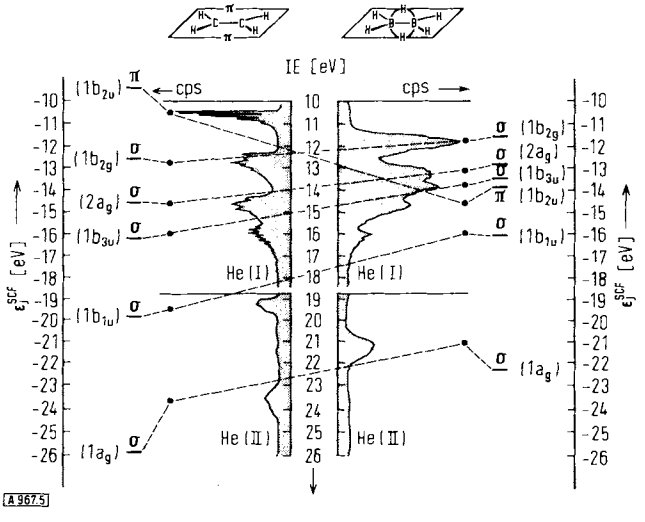
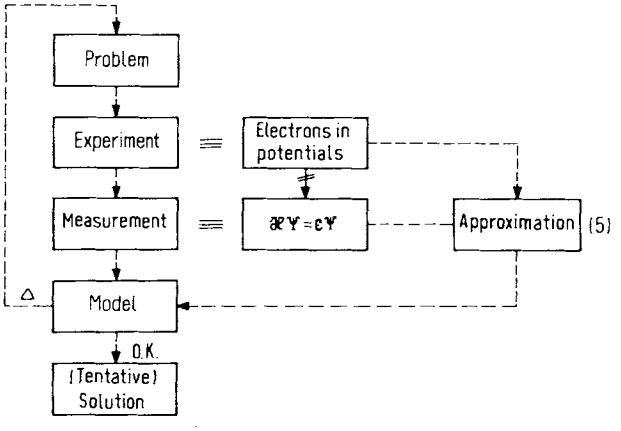


Fig. 5. Comparison of "*ab initio*" orbital energies, ε_j^{SCF} (eV) [—] and the vertical ionization energies IE_n^v (eV) [•] in the He(I)/He(II) PE spectra of ethylene and diborane [5].

Clearly, the PE spectroscopic vertical ionization energies—the energy differences between molecular ground state and the resultant radical cation state—allow a satisfactory correlation with calculated orbital energies (cf. Fig. 1). Thus the intimate symbiosis with the new experimental methods of PE spectroscopy establishes still further the utility of MO models and increases their trustworthiness. Starting from the diborane bonding problem, the PE spectra were measured and a plausible assignment achieved by means of MO models of comparable electronic systems; this cycle is simultaneously an example of how MO models are increasingly drawn upon today in the interpretation and rationalization of measured data which taken alone would be generally uninformative (5)[6]



As "their own computer", molecules print out in the form of measured data complete solutions of the Schrödinger equation, which is not capable of closed solution for many-body systems. Approximate calculations and the models deduced from them increase in usefulness the more closely they can be directly correlated with experimental data. Photoelectron spectra, which permit *via* Koopmans' theorem a "quasi" reading off of orbital energies, are an exceptionally appropriate starting point for MO studies. These frequently lead, as should be demonstrated in the following, to a better conceptualization of "Bonding in Molecules", and with that also of other molecular properties.

2. Electron Delocalization in Boron Compounds

The PE spectrum of diborane was discussed with a qualitative MO model which, starting from ethylene, assumed a diprotonated or four centered π bond perpendicular to the molecular plane. The thus described electron delocalization, which reduces the electron deficiency at the boron center, at the same time can be drawn upon as an explana-

tion for the dimerization of monoborane BH_3. The chemist universally accepts the unoccupied virtual boron $2p_z$ orbital, whose energy in calculations is placed[7] a few electron volts above the carbon π_z orbitals, as the unifying thread through the physical properties and reactions of boron compounds of coordination number 3[8]. Besides the stabilization with an increase in coordination number through formation of multi-centered bonds as in boron hydrides or through formal octet completion as in Lewis acid/Lewis base complexes, a π type electron back bonding $>\overset{\curvearrowleft}{B}-X$, perpendicular to the molecular plane has also been discussed for filling the boron electron-hole. Numerous observations on boron compounds, such as planar molecular frameworks, unexpectedly small dipole moments or relatively high rotational barriers $>B-\overset{\curvearrowleft}{\ddot{}}-X$, find their easiest interpretation in this way[8]. What information about charge distribution and bonding in ground state trigonal planar boron compounds does PE spectroscopy furnish?

In the series of boron compounds $R_2B\dot{X}$, $RB\dot{X}_2$, $B\dot{X}_3$, in which the neighboring atom $\dot{X}$ exhibits an electron pair n_X of π symmetry an occupied bonding π_b orbital with decreasing orbital energy as well as none, one, or two occupied nonbonding orbitals respectively of equal energy are anticipated according to qualitative MO models (Fig. 6). These expectations are fully met in the photoelectron spectra[9] of the (dimethylamino)methylboranes $(H_3C)_{3-n}B[N(CH_3)_2]_n$.

From the PE spectrum of trimethylborane given for comparison, one gathers that the ionizations from the BCH framework only occur above 10.5 eV. The PE bands at lower ionization energies are to be assigned on this basis to the bonding and nonbonding π electrons. As expected, the ionization energy $IE^v(\pi_b)$ increases with increasing number n of substituents X, and the approximate intensity ratios of the bands $\pi_{nb}:\pi_b$ amount to 1:1 for $n=2$ and 2:1 for $n=3$. Especially instructive is the change from tris(dimethylamino)borane, whose BN π bonds are twisted in a propeller-like fashion by some 30° to the ring-flattened π system of triazaboradecalin because of the steric demands of the methyl groups. As a consequence of better overlap, the π delocalization becomes greater and the π_b ionization energy increases by about 0.9 eV. As expected, the π_{nb} band remains nearly constant and is broadened because the different alkyl substitution—$N(CH_2—)_2$/—$NH(CH_2—)$ removes the π_{nb} degeneracy[9].

In the general case of planar BX_3 compounds with at least local D_{3h} symmetry, the degenerate π_{nb}-orbital belongs to symmetry type e'' and the π_b orbital to a_2''. The difference ΔIE_π in the PE ionization potentials thus assigned reflects the dependence of π stabilization on the substituent X (Fig. 7).

In Fig. 7 the BX_3 molecules are arranged according to increasing π_{nb} ionization potential. An increasing π splitting is found for $S \approx O < N$ and $I < Br < Cl < F$. As a rough approximation, it is to be expected that with comparable overlap the π interaction should increase with decreasing energy gap between the electron pair n_X and the unoccupied p_B boron orbital, for example $\Delta\pi_N > \Delta\pi_O$. With a comparable energy gap between n_X and p_B, the π interaction increases with better overlap, for example $\Delta\pi_O > \Delta\pi_I$. Finally in a comparison of BCl_3 with BF_3, $\Delta\pi_{Cl}$ is smaller than $\Delta\pi_F$,

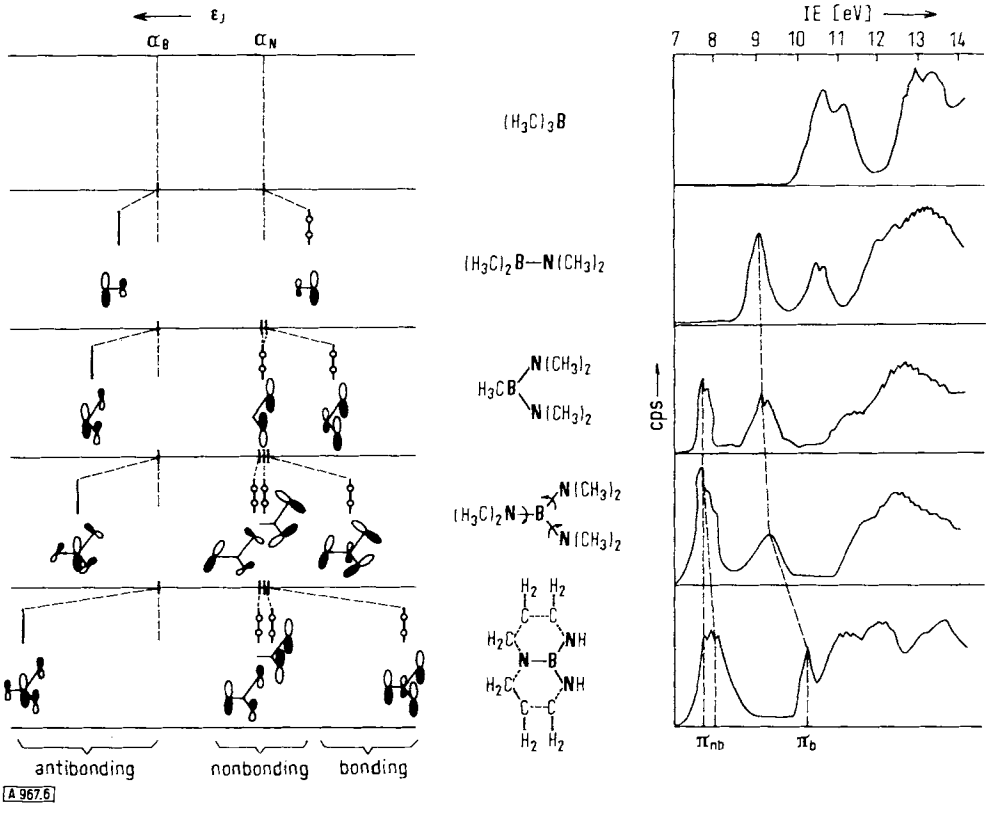


Fig. 6. Qualitative MO models for π delocalization in boron compounds $R_{3-n}BX_n$ and PE spectra in the 7—14 eV region for trimethylborane, (dimethylamino)methylboranes, as well as triazaboradecalin (2,6,10-triaza-1-borabicyclo[4.4.0]decane) [9].

even though n_{Cl} lies more than 4 eV higher than n_F, which demonstrates the limitations of an exclusively π argument. It is known that fluorine substituents lower σ orbitals by several electron volts because of their strong σ electron withdrawing interaction, but that because of an opposing

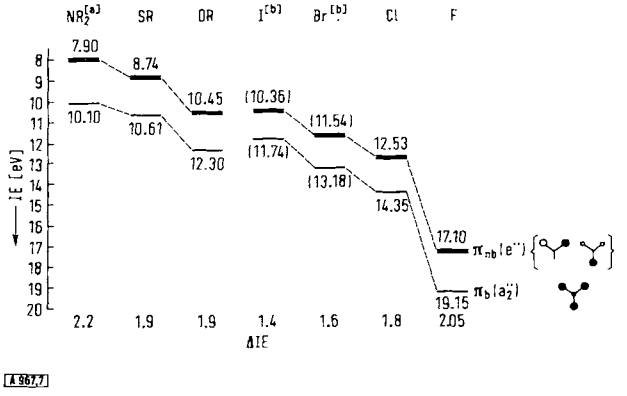


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Fig. 7. PE ionization energies of BX_3 compounds [9—11].
[a] triazaboradecalin. [b] spin-orbit coupling.

donor interaction the π orbitals are only slightly affected. BF_3 can be regarded as a special example of this "perfluoro effect" in which the large inductive effect of three fluorines at a single center lowers the vacant boron 2p orbital sufficiently to allow strong π back bonding by n_F, $\ddot{F}\overset{\frown}{\leftarrow}B$.

The π splitting from the PE spectra of the boron trihalides (Fig. 7) permits rationalization of further molecular properties. Thus, *inter alia*, the order of decreasing Lewis acidities $BI_3 \approx BBr_3 > BCl_3 > BF_3$[7,11,12] may be the result of the loss of π stabilization energy[7,11] in the order $BI_3 < BBr_3 < BCl_3 < BF_3$ which is important in determining the position of the equilibrium:

$$X_3B + :D \rightleftharpoons X_3B{-}D$$

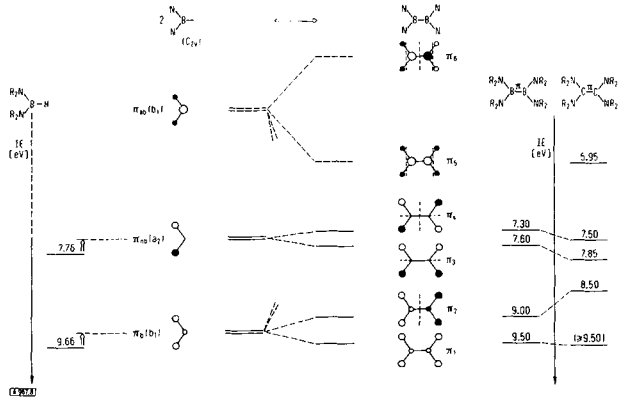

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Fig. 8. Molecular orbitals of the $(R_2N)_2BH$ π system, their symmetry-adapted combination to the molecular orbitals π_1 to π_6 of $(R_2N)_2E{-}E(NR_2)_2$, and comparison of the PE ionization energy of tetrakis(dimethylamino)diborane(4) and -ethylene [13]. (All orbital diagrams as bird's-eye views.)

Next, the compounds $(R_2N)_2E{-}E(NR_2)_2$ with E = B,C should serve as another example along the way, which illustrates not only the utility of PE spectroscopy in comparison of related molecules, but also the construction of MO models through symmetry-adapted combinations of partial systems characterized by PE spectroscopy. The π system of bis(dimethylamino)boranes, $(R_2N)_2BR$, presented in Figure 7 is the point of departure. For R = H from the PE spectrum one obtains a splitting $IE_{\pi_b} - IE_{\pi_{nb}} = 9.66 - 7.76 = 1.9$ eV. Union at E—E of the $(R_2N)_2E$ building blocks yields in a transparent fashion the desired molecular orbitals of $(R_2N)_2E{-}E(NR_2)_2$, π_1 to π_6 (Fig. 8). The starting orbitals π_b and π_{nb} from $(R_2N)_2BH$ were combined in Figure 8 on the assumption that they are inductively raised on exchange of H for the two $B(NR_2)_2$ groups, and that the π_6 (b_1) interaction with the symmetry equivalent $\pi_{ab}(b_1)$ orbital produces negligible intermixing because of the large orbital separation $E\pi_{ab} - E\pi_b$. This results in orbitals of increasing nodal number with predominate or exclusive N character, the B—B contribution being minute and the resultant splitting of the pair π_1/π_2, as well as π_3/π_4, only slight. In contrast to tetrakis(dimethylamino)diborane(4), the ethylene derivative possesses two more electrons, which occupy π_5. This orbital ought to be strongly lowered due to the substantial π_{ab} splitting, in keeping with the dominant C—C character. Within our MO picture, the fine differences in the vertical ionization energies allow parametrization such that the interaction C—N is smaller than B—N and as a result the splitting of the starting orbitals π_b/π_{nb} decreases, whereas the splitting π_1/π_2 increases because the interaction C—C is greater than B—B.

The qualitative MO model for the π systems $N_2E{-}EN_2$, developed on the basis of PE spectra (Fig. 8), permits additional properties of the molecules $(R_2N)_2E{-}E(NR_2)_2$ to be understood. Thus tetraaminoethylene reacts with C—C cleavage to form metal-diaminocarbene complexes, and because of ready electron donation functions as a strong reducing agent with formation of radical cations and dications. For the diboron derivative, a dianion is predicted with a shortened B—B bond[13].

Is borazine, $B_3N_3H_6$, an "inorganic benzene"? This apparent problem, a subject of much discussion[8c], arises from the isosteric relationship between the two compounds, which can be illustrated by comparison of the PE spectra, and will at the same time close this Section on electron delocalization in boron compounds. The point of departure is the PE spectrum of benzene (Fig. 9), whose bands of lower ionization energies are assigned as specified to the five highest occupied molecular orbitals[14a]. On going to borazine, the symmetry D_{6h} is reduced to D_{3h}, whereby according to symmetry correlation tables[15], the following symmetry transformations occur:

			D_{6h}	→	D_{3h}
π:	e_{1g}	and	e_{2u}	→	e″
	b_{2g}	and	a_{2u}	→	a_2''
	e_{2g}	and	e_{1u}	→	e′

(6)

Within a qualitative MO model this means that additional splitting is to be expected for each of those molecular orbitals which then belong to the same symmetry type as a result of the symmetry lowering $D_{6h} \rightarrow D_{3h}$—compare for example the arguments pertinent to Figure 4 or 8. Thus the bonding π-orbitals 1e″ and $1a_2''$ (previously $1e_{1g}$

and $1a_{2u}$) should be depressed through the interaction with the antibonding π orbitals 2e'' and $2a_2''$ (previously $1e_{2u}$ and $1b_{2g}$). By contrast, the occupied σ orbital 4e' must remain nearly constant as a result of being bracketed by three σ bonding and 4 antibonding σ^* orbitals of equivalent symmetry type e'[16a]. As Figure 9 shows, these expectations are entirely fulfilled.

The orbital sequence $\pi/\sigma/\pi$ in borazine, as has been proposed proceeding from the isoconjugate six-membered rings on the basis of symmetry-adapted perturbation arguments[16a], finds numerous confirmations in the PE spectra: the ring vibrational fine structure[16a,b,18], the Jahn-Teller splitting[16b,18] of the states corresponding to the doubly degenerate orbitals π_2(1e'') and σ_8(4e'), and the approximate intensity ratios of 2:2:1 in the first three bands. The π splitting amounts to 2.74 eV (2.99 eV in benzene).

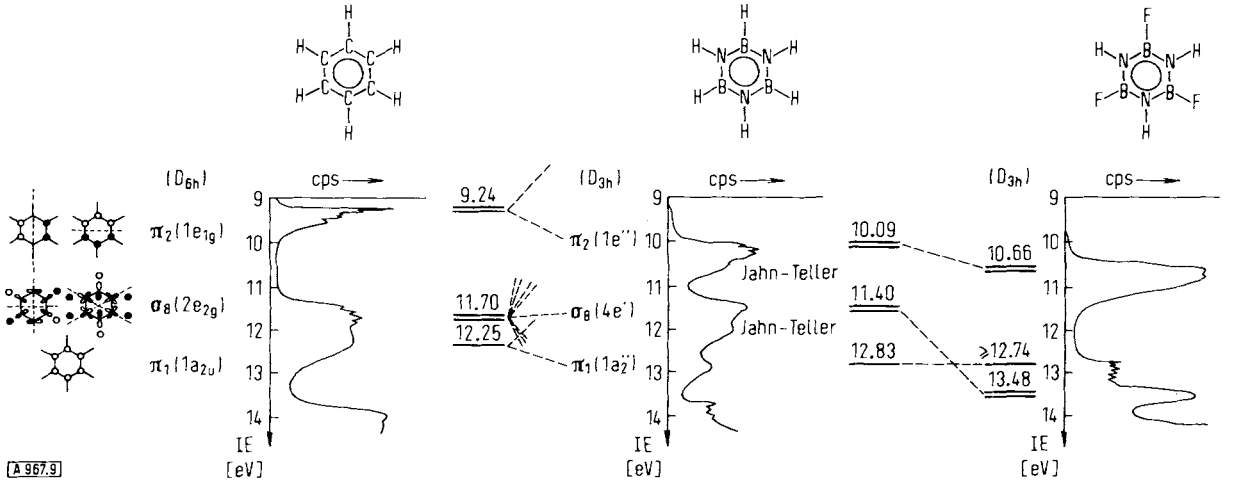


Fig. 9. PE spectra in the region 9—14 eV of benzene [14], borazine [16a], and *B*-trifluoroborazine [17a] with band assignments.

An "*ab initio*" calculation yields the same orbital sequence[17]. Comparison with the PE spectrum of *B*-trifluoroborazine furnishes additional arguments[16b,18]. As already discussed for BF_3, the fluorine substituents increase the σ ionization energies, whereas the π ionization energies remain nearly constant. A comparison of the PE spectra of borazine and its *B*-trifluoro derivative shows that the σ ionization energy increases by about 2.08 eV. At the same time the intensity ratios of the first three bands change from 2:2:1 to 2:1:2. The perfluoro effect thus confirms the orbital sequence $\pi/\sigma/\pi$ for borazine and thus also the similarity with benzene.

Looking back, Section 2 contained further examples of how connections between related molecules become visible in their PE spectra, and how this simultaneously facilitates the assignment of spectra. For these purposes, compounds with trigonal planar boron are didactically excellent, because a π system follows as a consequence of the boron electron deficiency. These π systems are satisfactorily described with MO models whose orbital energies can be correlated by Koopmans' theorem with vertical ionization energies which we measure as energy state differences. Although the discussion of boron trifluoride showed how arbitrary the model subdivision of molecules can be, in many planar molecules π and σ electrons can obviously be separated to a good approximation. Therefore, π and σ systems of selected carbon and silicon compounds will next be treated separately.

3. π and σ Interactions in Carbon and Silicon Compounds

Elements of Group IVB differ from the electron-deficient element boron in that the number of valence electrons corresponds to the number of valence orbitals. In discussions of their compounds this has lead to an overemphasis of the so-called "bond model". The bond line, as the topological symbol for the connection between atoms, has been identified with two electrons, and the molecule described in this way with localized bonds. On the other hand, for example, the bond enthalpy parameters derived from heats of formation are not strictly additive even for isomeric hydrocarbons[19a] and as might be expected cannot be correlated with mass spectroscopic dissociation energies.

3.1. PE Splitting Patterns for Ethylene π Units in Different Molecular Frameworks

The PE spectrum of planar ethylene (Fig. 5) was assigned with a molecular orbital model (Fig. 4) which established an occupied π molecular orbital with the usually accepted σ-π separation. Extending this assumption, to what extent can the PE splitting patterns of larger π systems (Fig. 10) be interpreted in terms of interactions between small π units such as these?

For a detailed discussion of the PE spectra of the hydrocarbons in Figure 10, the reader is referred to the original work largely carried out by *Heilbronner et al.* Neglecting the σ contributions (cf. Section 3.3), an attempt will be made in a simple model to clarify their π ionization energies (Fig. 10) by means of the different spatial arrangements and symmetry types of the π molecular orbitals. For a better overview, we differentiate between three groups:

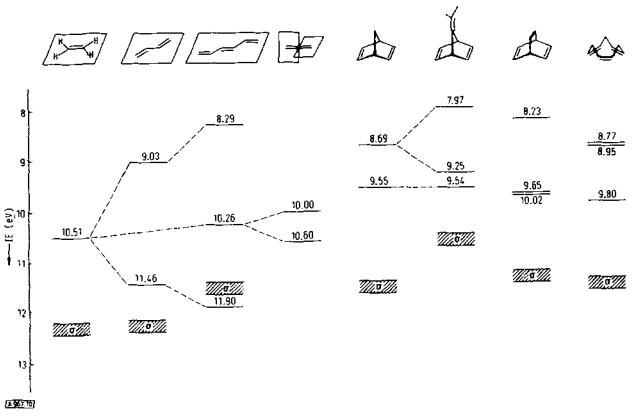
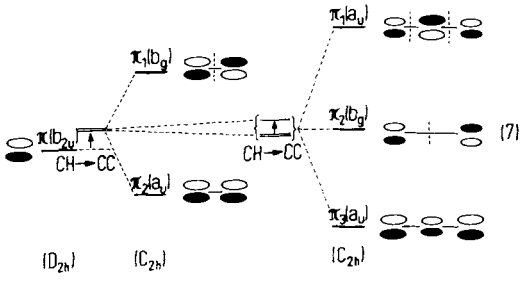


Fig. 10. Vertical π-ionization energies IE^v (eV) of ethylene [2a, 5], s-*trans*-butadiene [2b, 20], all-*trans*-hexatriene [20], allene [21, 2a], norbornadiene [22—24], 7-isopropylidenenorbornadiene [23, 24], barrelene [25], and trishomobenzene [22, 26].

planar conjugated, linear cumulated, and nonneighboring through space interacting ethylene π systems.

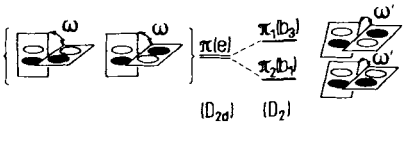
The planar alkenes $H(HC{=}CH)_nH$ exhibit a PE splitting pattern[20] (Fig. 10), which is describable in a clear fashion through a linear combination of occupied ethylene π orbitals:



(7)

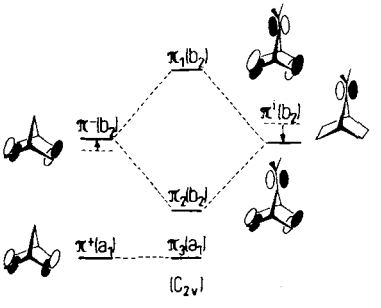
In the MO model (7) the coupling of two ethylene molecules raises the π center of gravity because of the replacement of each CH by a common C—C bond[20]. This then splits into a bonding (C_{2h}:a_u) and an antibonding (b_g) linear combination; the interaction parameter, $\beta = -1.22$ eV, follows from the PE ionization energy difference, $\Delta IE_\pi = 2.43\,\text{eV} = 2|\beta_\pi|$. In hexatriene one must proceed formally from two different ethylene π units; of these, the C—C bonded on both sides should be raised still further. After "switching on" the π interaction, the nonbonding MO $\pi_2(b_g)$, with a nodal plane through the central bond, remains unaltered, whereas the two a_u molecular orbitals show a splitting of $IE_{\pi_3} - IE_{\pi_1} = 3.61$ eV ($\beta_\pi = -1.2$ eV[20]). Notice that in the PE spectrum of hexatriene a σ orbital is inserted between π_2 and π_3 (Fig. 10).

The spectrum of linear allene with two crossed ethylene π units exhibits two PE π bands at 10.0 and 10.6 eV[2a], whose π center of gravity 10.3 eV corresponds closely to that of butadiene. The splitting $\Delta IE_\pi = 0.6$ eV results from



(8)

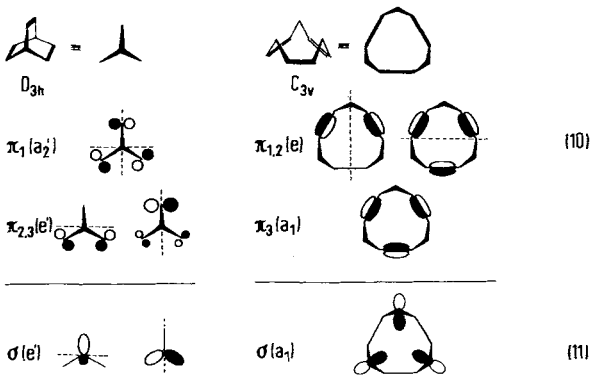
a Jahn-Teller twisting deformation of the radical cation ($D_{2d} \rightarrow D_2$)[21], which lifts the degeneracy of the MO's made up of the mutually perpendicular, noninteracting π units. In the MO model (8) the decrease[21] of the twist angle (calc. $\omega' \approx 38°$) leads to a bonding (D_2:b_1) and an antibonding (b_3) π MO. Of the corresponding radical cation states, the one with doubly occupied bonding π orbitals $(\pi_2)^2(\pi_1)^1$ is more stable than that with the occupancy $(\pi_2)^1(\pi_1)^2$. The interaction of non-neighboring ethylene π moieties through space[27,22] appears especially clear and impressive in a comparison of the PE spectra of norbornadiene[22—24] and 7-isopropylidenenorbornadiene[23,24]. Starting from the two lowest vertical ionization energies of norbornadiene, in a MO model (9) with neglect of σ mixing[26], the electrons may approximately be assigned to the linear combinations π^- and π^+ (C_{2v}: b_1 and a_1):



(9)

Proof for the sequence $IE_{\pi^-} < IE_{\pi^+}$ and, at the same time, another example of splitting between non-neighboring orbitals of the same symmetry type are provided by the ionization energies of 7-isopropylidenenorbornadiene (Fig. 10), which is discussed in a π MO scheme (9) as follows. The arrows designate modification of starting orbitals. Thus, as a result of the increase in size of the C molecular framework of norbornadiene, both the highest occupied σ orbital and the π center of gravity are raised[24,28]. At the same time, the introduction of double bonds into the C molecular framework of 7-isopropylidenenorborane lowers the orbital $\pi^i(b_2)$[24,29]. Interaction is possible only between orbitals of the same symmetry type. Thus, the MO $\pi_3(a_1)$ corresponds to the unchanged starting orbital $\pi^+(a_1)$, whereas $\pi^-(b_2)$ and $\pi^i(b_2)$ mix to form the MOs $\pi_1(b_2)$ and $\pi_2(b_2)$. The "through space" interaction parameter, $\beta_\pi = -\Delta IE_\pi/\sqrt{2} = -0.45$ eV, is comparable to that of norbornadiene[24] and, as expected, smaller than that for direct conjugation, for example in butadiene ($\beta_\pi = -1.22$ eV).

In closing, the π systems of barrelene and trishomobenzene should be compared. These contain in different molecular geometries (D_{3h} and C_{3v}, respectively) three double bonds separated from each other by a tetrahedral carbon center. Their PE spectra exhibit different splitting patterns (Fig. 10) in which the Jahn-Teller-split double maximum appears once as the second and once as the first PE band. Assuming that the through space π interaction dominates in these molecules too, the qualitative π MOs (10), ordered according to increasing number of nodes, permit rationalization of the PE spectroscopically secured sequences $\pi_1(a_2')/\pi_{2,3}(e')$ and $\pi_{1,2}(e)/\pi_3(a_1)$.



(10)

(11)

The additional σ MOs sketched out in (11) should point out here (cf. Section 3.3) that in three-dimensional molecular frameworks π and σ orbitals of the same symmetry type are generally present and will mix with each other to a greater or lesser extent an exception, for example, is π(a'2) of barrelene[25]). Apart from this, however, the π splitting in the PE spectrum of trishomobenzene is in aggreement with the concept of homoaromaticity suggested by *Winstein*[30] for rings with $2n+1$ π units of the same symmetry type and of similar energy[26], with $4n+2$ electrons in accordance with the Hückel rule. However, as is to be expected, a special homoaromaticity cannot be measured[19,26], and the homoconjugative splittings, *e. g.* in cycloactatetraene[29] with 2n π units, are of the same order or larger.

As shown in the previously discussed PE spectra of unsaturated hydrocarbons, π conjugation is consequently not limited to neighboring double bonds. π units separated by a tetrahedral carbon[30a] also conjugate in molecules of appropriate geometry. Here, a useful concept in qualitative MO models, *viz.* that only orbitals of the same symmetry can interact, becomes especially clear. Increasing C_π—C_π distance between the interacting units leads to a decrease in splitting. Examples of this are benzene ($d_{C_\pi C_\pi} = 1.4$ Å, $\Delta IE \approx 3$ eV) and trishomobenzene ($d_{C_\pi C_\pi} = 2.2$ Å, $\Delta IE \approx 0.9$ eV)[27], for which similar PE splitting patterns can be predicted from orbital symmetries, independent of the value of the π splitting (Figs. 9 and 10).

In three-dimensional molecular frameworks, such as trishomobenzene, "σ orbitals" of π symmetry[10]type can mix with π orbitals. But before a discussion of this σ-π interaction, it should be investigated first how far the MO model developed with π systems can be applied to σ systems.

over the molecular framework. Predictably, therefore, the data can be satisfactorily understood in terms of different MO models[31]. Here an approximation closely related to the discussed PE splitting pattern of π units is preferred, which considers interactions exclusively between bonding orbitals[20,27,31]. This so-called LCBO (linear combination of bond orbitals) MO model[31] proves to be especially useful[20] in interpretation of PE spectra, in spite of its inherent simplifications[27], because it may be more straightforwardly parametrized from PE spectra.

The He(II) spectrum of methane[2b] shows two bands; one between 12.6—16 eV with a center of gravity at 14.2 eV, with apparent threefold Jahn/Teller splitting[32] due to the change in molecular geometry of the radical cation ($T_d \rightarrow D_{2d}$[32]→...), and a second one near 23 eV. The molecular orbitals of the LCBO model (Fig. 11) follow from the known rule that their number of nodes increases with increasing orbital energy. The relative orbital energies can be estimated with the help of an approximate formula[*][19b,32].

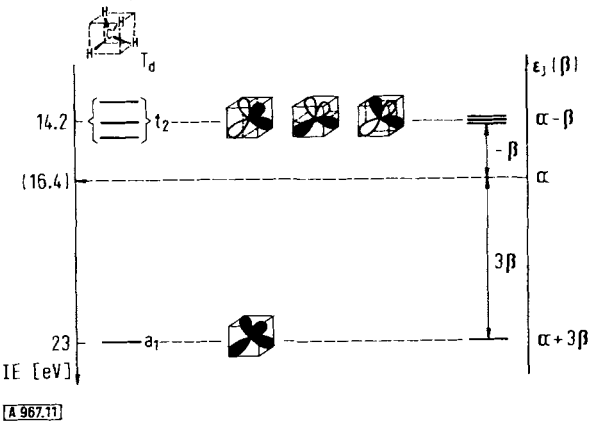
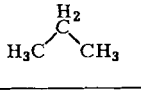
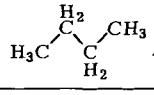
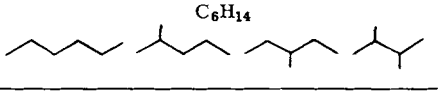


Fig. 11. PE ionization energies of methane and parametrization of a CH bond orbital model [*].

As can be seen in Figure 11, one MO without nodes at $\varepsilon_1 = \alpha + 3\beta$[*] and three degenerate MOs each with one node at $\varepsilon_{2,3,4} = \alpha - \beta$[*] result. Comparison with the PE ionization energies *via* Koopmans' theorem (4) gives an orbital center of gravity $\alpha_{CH} = -16.4$ eV and an interaction parameter $\beta_{CH} = -2.2$ eV.

Alkane	CH_4	H_3C-CH_3				C_6H_{14}		
IE_1 [eV]	13.0	11.6	11.1	10.6	10.2	10.1	10.1	10.0

(12)

3.2. Bond-Bond Interactions in Alkanes and Silanes

It has been long known that mass spectroscopic ionization potentials of alkanes decrease with increasing chain length and increasing branching[31].

This experimental result suggests that in the resultant alkyl radical cation the positive charge is significantly delocalized

[*] For systems with equivalent starting orbitals, the approximate eigenvalues $\varepsilon_j^0 = \alpha + x_j^0\beta$ (where x_j^0 is the splitting relative to the orbital center of gravity in units of β) are given by the following[19b,33]: The eigenvalue coefficient $x_j^0 = 2\left(\frac{1}{n_j}\right)(Z_{b,J} - Z_{ab,J})$ is obtained from the number of starting orbitals n_j in molecular orbital J as well as the number of bonding $Z_{b,J}$ and antibonding $Z_{ab,J}$ interactions between them. For the LCBO molecular orbital of methane one obtains, $x_1^0 = 2(\frac{1}{4})(6-0) = +3$ and $x_{2,3,4}^0 = 2(\frac{1}{4})(2-4) = 1$ (cf. Fig. 11).

The example of methane not only demonstrates how easy it is to parametrize LCBO models. It also shows that with the previously mentioned assumption of four C—H bonds containing four equal and independent bonding electron pairs important molecular properties remain unexplained. Finally, the observed[2b] band intensities $t_2:a_1=7:1$ (instead of 3:1), which would have to be explained[26,34] by a predominant C(2p) contribution with larger cross section to the t_2 orbital and predominant $C(2s_1)$ contribution to the a_1 orbital, also point out the limitations of models with isolated equivalent bonds[*].

The electron delocalization[**] in σ molecular frameworks becomes especially clear in a comparison of the PE spectra of permethylpolysilanes and their interpretation by simple MO models[35]. Hexamethyldisilane ($Me_3SiSiMe_3$) exhibits a well separated PE band at 8.69 eV in its spectrum, which can be assigned as an ionization from a predominantly Si—Si bond molecular orbital. In the region 7.5—10 eV open-chain, branched, and cyclic polysilanes (—Si—Si—) possess characteristic PE splitting patterns (Figure 12) as would be expected from the topology of the Si—Si bond framework.

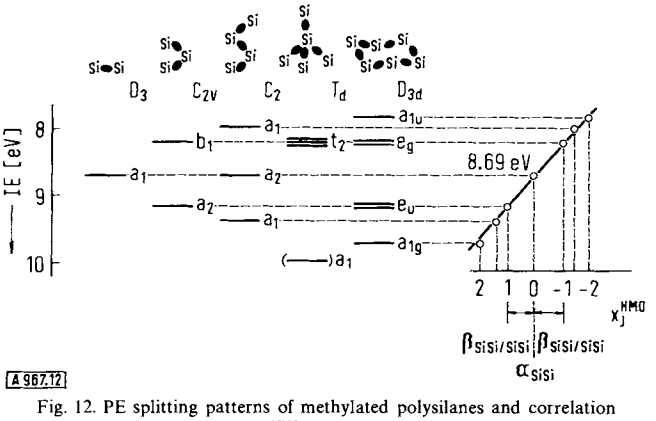


Fig. 12. PE splitting patterns of methylated polysilanes and correlation with eigenvalue coefficients x_j^{HMO}.

With the different splittings, the center of gravity of the Si—Si molecular orbitals (8.69 eV) remains approximately constant, so that the SiC and CH orbital contributions can be neglected, except in so far as they are absorbed into the hexamethyldisilane standard. For this correlation Hückel MO eigenvalues (orbital energies) $\varepsilon_j^{HMO}=\alpha+x_j^{HMO}\beta$ (cf. [**]) are used. The PE parametrization can be carried out in this case directly from the first ionization potential of hexamethyldisilane IE_1 ($Me_3SiSiMe_3$) = 8.69 eV = $-\alpha_{SiSi}$ ($x_j^{HMO}=0$); the interaction parameter $\beta_{SiSi/SiSi}=-0.5$ eV is obtained from the slope of the regression line drawn in Figure 12. In conclusion it may be noted that numerous other properties of polysilanes, such as the decreasing electronic excitation energy of open-chain derivatives $R—(SiR_2)_k—R$ with increasing chain length k, are explained with σ electron delocalization[35].

The PE spectra of polysilanes (Fig. 12) are, as a consequence of the low ionization potential of the Si—Si bond, an especially illustrative example of the utility of σ MO models. In particular for molecular frameworks of high symmetry, these models can be broadened to accommodate the general case in which mixing between different bond types cannot be neglected. Thus the PE spectrum of neopentane can be assigned on the basis of a LCBO model similar to that of Figure 11 with symmetry-adapted combinations of CC and CH bonding orbitals[36]. Returning to the starting point, it becomes understandable that the first ionization potential of linear or branched alkanes C_nH_{2n+2} must decrease[37] with increasing n, *i.e.* an increasing number of starting orbitals[19d,31].

LCBO models are frequently advantageous for the description of σ molecular skeletons, even though they neglect the possible mixing in of unoccupied orbitals, because they may be easily parametrized with the aid of PE ionization energies. At the same time, an important contribution of photoelectron spectroscopy to our knowledge of molecules becomes apparent: σ molecular skeletons are finally more accessible to measurement.

3.3. π-σ-Conjugation

In the preceding sections, π-π and σ-σ interaction models were introduced on the basis of the PE ionization energies of selected hydrocarbons and alkylsilanes. Here, it was pointed out that conjugation between π bonds is not restricted to planar systems with neighboring π centers, but that depending on molecular geometry and symmetry type of the π starting orbitals, "through space" interactions may also result. Further on in the discussion of MO models for three dimensional unsaturated molecules, it was shown that the π orbital center of gravity did not depend only on the composition of the molecules compared with each other (cf., *e. g.* (9): differing alkyl group size or increasing number of π bonds), but was significantly determined by the available "σ-orbitals" or π symmetry (cf., *e.g.*, (10) and (11)). In the following, this extension of the π conjugation concept to symmetry-allowed π-σ interactions, termed "hyperconjugation" by *Mulliken*[38] and summarized under through bond coupling effects by *Hoffmann*[27], will be explained in greater detail utilizing additional spectroscopic results.

For an example of the application of a hyperconjugation model, we can draw upon the methylacetylene PE spectrum[2a] which can be assigned, with assumption of a splitting between the degenerate π orbitals of the rotationally symmetric acetylene π system and the degenerate π orbitals of the methyl group[39] (Fig. 13).

For the starting orbitals we use the first ionization potentials of acetylene $IE_1(HC{\equiv}CH)=11.4\,eV\equiv-\alpha_{C\equiv C}$ and of methane $IE_1(CH_4)=14.2\,eV\equiv-\alpha_{CH_3}$ because three CH bonding orbitals under local C_{3v} symmetry with $\alpha_{CH}=-16.4$ eV and $\beta_{CH/CH}=-2.2$ eV should split to give the CH_3

[*] In the LCBO model of methane the three highest occupied orbitals are of symmetry t_2 and can contain only the p_C atomic orbital. The low lying a_1 molecular orbital contains only the s_C atomic orbital.

[**] In general each linear combination of a set of occupied orbitals leads to exactly equivalent calculation results [3b]. Clearly the labor and expense of the calculation decreases with a proper choice of starting orbitals. A set of occupied orbitals may readily be transformed into another without changing the total energy (see, for example, the discussion of methane in [19a]). Thus bonds may be localized or delocalized. Such equivalent MO models are differentiated only in their application to the explanation of specific molecular properties.

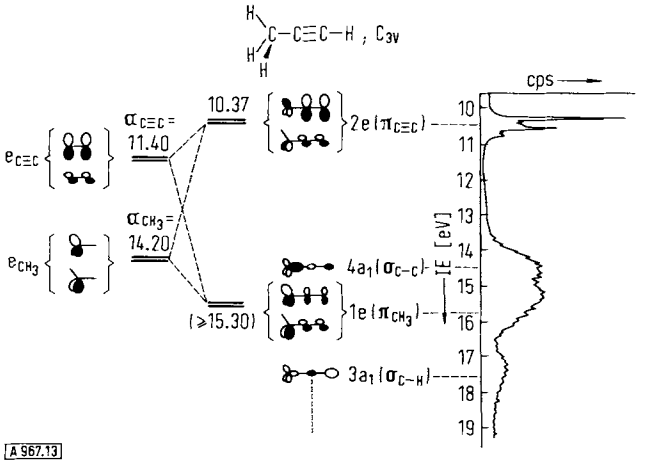


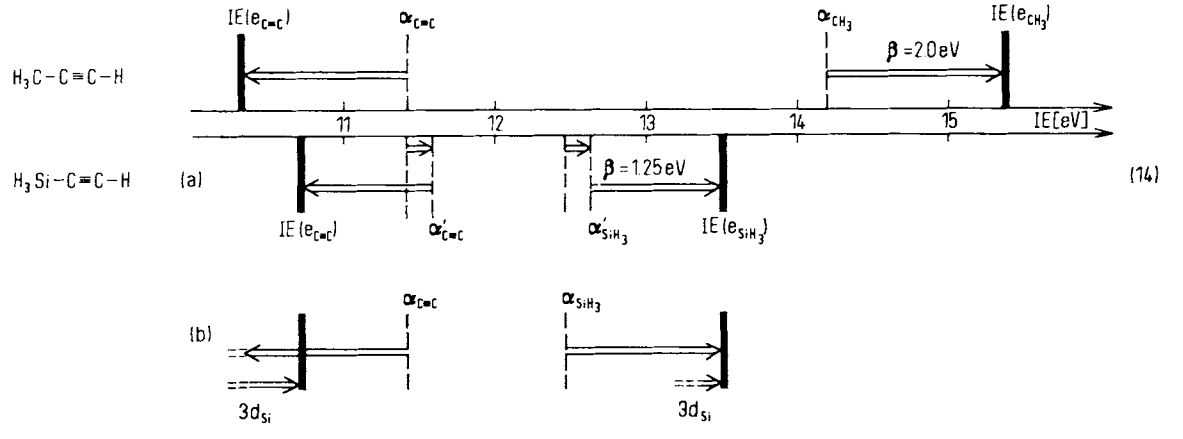
Fig. 13. Hyperconjugation model $e_{C\equiv C}/e_{CH_3}$ and PE spectrum of methylacetylene [2a].

group orbitals e and a_1 at -14.2 eV and -20.8 eV (Fig. 11). The hyperconjugation parameter $\beta_{C\equiv C/CH_3}$ can be calculated as follows from the PE ionization energy[39].

$$\begin{vmatrix} \alpha_{C\equiv C}-\varepsilon & \beta_{C\equiv C/CH_3} \\ \beta_{C\equiv C/CH_3} & \alpha_{CH_3}-\varepsilon \end{vmatrix} = 0$$

$$\beta_{C\equiv C/CH_3} = -\sqrt{(IE_1^{HC\equiv CH}-IE_1^{H_3C-C\equiv CH})(IE_1^{CH_4}-IE_1^{H_3C-C\equiv CH})}$$
$$= -2.0\,\text{eV}$$

A comparison is interesting with silylacetylene $H_3SiC{\equiv}CH$[39] whose first ionization potential $IE_\pi = 10.73$ eV is some 0.4 eV greater (!) than that of the methyl derivative. Parametrization is possible with $\alpha_{SiH_3} \equiv -12.45$ eV the average ionization potential of the e_{1g} and e_{1u} orbitals of disilane[39]. After a necessary 0.16 eV correction to the π center of gravity, the relatively smaller (compared to CH_3 hyperconjugation) parameter $\beta_{C\equiv C/SiH_3} = -1.15$ eV is obtained. Diagram (14) compares the π ionization potentials (|) and the hyperconjugation parameters (:) for methyl- and silylacetylenes:



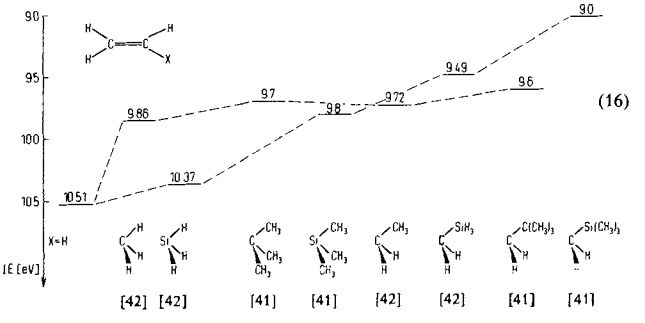
as $3d_{Si}$ or $4p_{Si}$ (14b), can only be defined in corresponding LCAO MO calculations (cf. *e. g.*[39] and particularly[40]). Nevertheless, the PE spectroscopic parameters (14) demonstrate that in spite of a smaller orbital separation $\alpha_{XH_3} - \alpha_{C\equiv C}$ in the silicon compound the net interaction β is smaller over the longer bond length in accordance with reduced overlap. Beyond this, the utility of the PE parameters (14) can be illustrated, for example, through the prediction of the three π ionization potentials of the disubstituted acetylenes[39]:

$$IE_{1,3} = \frac{\alpha_{C\equiv C}+\alpha_{CH_3}}{2} \mp \sqrt{\left(\frac{\alpha_{C\equiv C}-\alpha_{XH_3}}{2}\right)^2 + 2\,\beta^2_{C\equiv C/XH_3}}$$
$$IE_2 = \alpha_{XH_3}$$

IE_1 ($H_3CC{\equiv}CCH_3$) calc. 9.62 eV, exp. 9.61 eV and

IE_1 ($H_3SiC{\equiv}CSiH_3$) calc. 10.40 eV, exp. 1046 eV.

Hyperconjugation models cannot often be so directly parametrized[37,40] as was the case for the two degenerate e orbitals of methylacetylene (Fig. 13). By way of example, in planar π systems, with $XR^1R^2R^3$ substituents each of the XR bonds may be resolved into a π and a σ component and π-σ orbital mixing treated in this way[40]. On the other hand, simple qualitative hyperconjugation arguments are also often useful, as can be shown by the following discussion of the first ionization potentials of alkyl- and silylethylenes[41,42].



(16)

Generally, parametrization of LCBO hyperconjugation models can incorporate only the total interaction of the XH_3 substituent. Further factoring, into inductive contributions or in the case of silylacetylene into compensating back bonding to unoccupied orbitals of π symmetry such

Hyperconjugation increasingly destabilizes a π orbital; the smaller the energy difference of the starting orbitals, the better they overlap and, what is most important, the greater is the electron density in that p atomic orbital of substituent atom X which couples the π_{CX} and σ_{XR} bonds. For example,

in (16) because of the comparable C components in the σ_{C-H} and σ_{C-C} bonds the effects of all alkyl substituents are of comparable size whereas in the sequence $\sigma_{SiH} < \sigma_{Si-C} < \sigma_{C-SiH} < \sigma_{C-SiC}$ the π ionization potentials decrease sharply. Coplanarity of the π_{CX} and σ_{XR} bonds is a requirement for hyperconjugative interaction. This conformational dependence is found both experimentally[*] and in SCF MO calculations[41,42]. These approximation calculations[41,42] however give the correct energy sequence of π ionization energies only if Si_{3d} orbitals are included in the calculation.

Finally, hyperconjugation between two π units and CH_2 bridges as a function of the angle between the π planes should be presented. The first two PE ionization energies of norbornadiene (Section 3.1: Fig. 10), which have been assigned by comparison (9) with the 7-isopropylidene derivative to the antibonding $\pi(b_2)$ and the bonding $\pi(a_1)$ linear combinations[22-24], are the starting points for this discussion. Here the dominating through space interaction leads to a natural orbital sequence according to increasing nodal number. The dihedral angle ω between the planes of the double bonds, which in norbornadiene equals 112°, widens with increasing methylene group number n in the $(CH_2)_n$ bridge. As a consequence, the π overlap and with it the π-π split each decrease, which increasingly stabilizes the antibonding $\pi_1(b_2)$ and destabilizes the bonding $\pi_2(a_1)$ (Fig. 14).

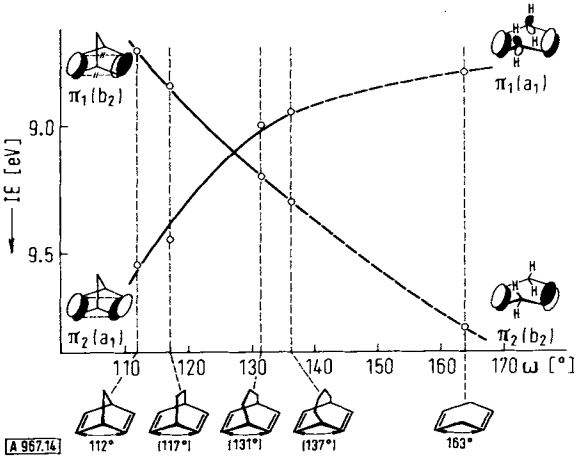


Fig. 14. Correlation diagram for through space-through bond splitting in 3,6-bridged 1,4-cyclohexadienes and 1,4-cyclohexadiene as a function of the dihedral angle ω [28].

For the $(CH_2)_3$- and $(CH_2)_4$-bridged cyclohexadienes, a π orbital sequence $\pi_1(a_1) > \pi_2(b_2)$ can be established by a comparison analogous to (9) of the spectra of bicyclo[3.2.2]nonatriene[43] and bicyclo[4.2.2]decatetraene[23] In 1,4-cyclohexadiene, dihedral angle $\omega = 163°$, the π

(17)

splitting reaches one eV[22-24]. The continuing rise of the bonding πa_1 molecular orbital and with this the reversal of the through space sequence $(\pi_1(b_2)/\pi_2(a_1) \Rightarrow \pi_1(a_1)/\pi_2(b_2)$ is traced back to increasing hyperconjugative destabilization of $\pi(a_1)$. The widening of the dihedral angle ω makes possible an increasingly stronger antibonding admixture of the σ orbital portion of π symmetry (Fig. 14).

This example should end the discussion which started with π-π splitting and proceed *via* σ-σ and π-σ interactions to π-σ-π conjugation. The simple models[44] introduced permit the approximate description of even three-dimensional molecules with π-σ mixing. These models are also supported by SCF MO calculations. He(I)/He(II) spectroscopy, which simultaneously furnishes all valence electron ionization potentials, has made important contributions to the development and verification of model concepts.

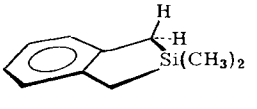
4. Molecules with Electron "Lone" Pairs

In the periodic system of the elements the ratio of the number of electrons to the number of available orbitals increases from left to right along each row. Within the nonmetals, the electron deficient element boron and the IVB elements C, Si... with half occupied (s,p) orbitals are followed by the Group V—VIII electron rich elements. These elements (V—VIII) possess, in their low coordination number compounds, "lone pair" electrons n_x on the atoms. The optimal distribution of regions of high electron density in a molecule is a structure determining factor, for example in the electron pair repulsion model of *Gillespie*[45]. Other possibilities for a favorable charge distribution in radical cations through electron pair delocalization will be discussed in the following on the basis of selected PE spectra.

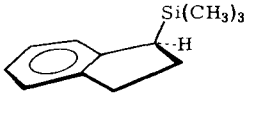
As a rule, PE spectroscopy is well suited for molecules with lone pair electrons n_X, for which in most cases there are characteristic bands in the region of low ionization energies. In an MO picture these are nonbonding electrons in a doubly occupied orbital, which ideally is localized on one center. Except where a high effective nuclear charge, as in fluorine, prevents it, these electrons are easily removed and lead to a needle like PE band (Figs. 2 and 3) which is all the sharper the greater the nonbonding character. Electron pair delocalization manifests itself therefore not only in a shift but usually also in a broadening of the PE band concerned.

We have already become aquainted with most of the MO models necessary for the interpretation of PE spectroscopic results in the preceding sections. Electron pairs n_X can usually be described in terms of p_X atomic or sp^n_X hybrid orbitals and often exhibit π symmetry character. In these

[*] An especially clear example is provided by the results of *C. G. Pitt* [J. Organometal. Chem. *23*, C 35 (1970)] for the indane derivative in which the silicon in each case occupies a β position to the benzene π system. However, where the silicon is fixed in the ring no hyperconjugation interaction of the Si—C bond is possible:



IE_1 = 8.41eV



IE_1 = 8.13eV

cases, the symmetry-determined π-π or π-σ MO models are applicable also to n_X-π, n_X-n_X, or n_X-σ interactions. It has been further pointed out that spin-orbit coupling is often easily observed for degenerate electron pairs of heavier elements. In the following, we shall discuss the PE spectra of molecules with electron pairs n_X, not element by element, but from a more general point of view, especially with regard to the use of particular MO models.

4.1. PE Spectral Correlation of the AH_2 Molecules Hydrogen Sulfide and Water

To begin with, the question to be pursued is: how can lone pair electrons be defined in MO models, and in what way do the pertinent PE spectra correspond with this? The PE spectrum of hydrogen sulfide[2a, 46] represents an example which is also educationally suitable for courses in general chemistry (Fig. 15).

gathered from the MO model of Figure 15, only one unique orbital of b_1 symmetry type exists, and therefore can not enter into bonding or antibonding combinations with other orbitals. In the MO approximation, a nonbonding "lone" or "free" electron pair can therefore be defined such that it must be describable by a single atomic orbital of a unique symmetry type.

Water is a further example of an AH_2 molecule with eight valence electrons. Among other things, it differs from H_2S because of a widening of the HAH bond angle to 105°, which in the MO correlation diagram (Fig. 15) leads to a destabilization of the $2a_1$, molecular orbital (a decrease in bonding interaction because of poorer overlap) and to stabilization of the molecular orbital $1b_1$ (an increase in bonding interaction because of better overlap)[47]. This expectation is confirmed by a comparison of the PE spectra of H_2O and H_2S (Fig. 15). The difference $IE_2 - IE_1$ decreases, and the difference $IE_3 - IE_2$ increases. The increase of the first ionization potential from 10.47 eV (n_S) to

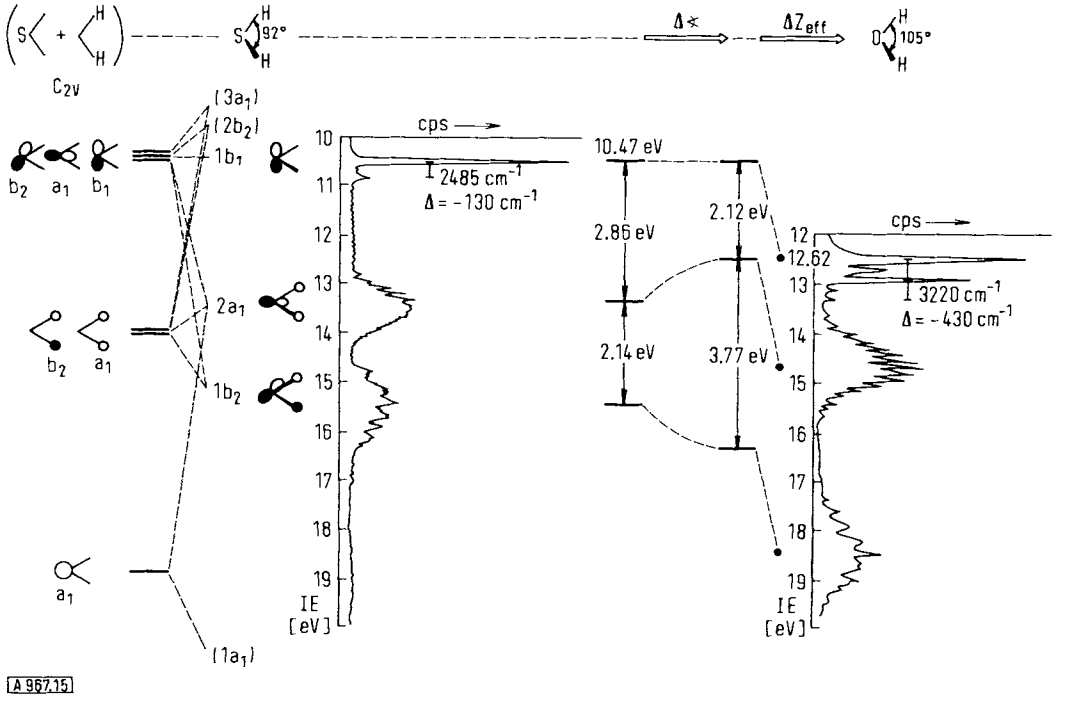


Fig. 15. PE spectra of hydrogen sulfide [2a] and water, and their interpretation in an AH_2 correlation diagram.

The six hydrogen sulfide molecular orbitals of symmetry $3\times a_1 + 2\times b_2 + b_1$ can be derived without difficulty from the symmetry-adapted combination of starting orbitals $3p_S$, $1s_H$, and $3s_S$ (Fig. 15)[19, 47]. Of the four occupied levels, only $1a_1$ with a predominant $3s_S$ contribution lies outside the He(I) measurement range. The indicated assignment can be supported by the pronounced vibrational fine structure[46]. The needle-like PE band at 10.47 eV is particularly interesting, because the vibration frequency due to the cation $H_2S^{\oplus}$ is lowered by only 130 cm^{-1} compared to the symmetric stretching vibration in the H_2S molecule. This PE spectroscopic result verifies that here a nonbonding electron was removed. As may be

12.62 eV (n_O) is caused by the higher effective nuclear charge of oxygen[48], which also polarizes the $O^{\delta-} \leftarrow H^{\delta+}$ bond and increases the charge density on oxygen ($\mu(H_2O) = 1.85$ D, $\mu(H_2S) = 1.10$ D). Within the electron pair repulsion model[45], the angle widening $H_2S \rightarrow H_2O$ can also be understood in this way. Finally both the large decrease in the bond stretching frequency of $-430\,cm^{-1}$ as well as the appearance at the same time of the deformation vibration referred to in Figure 15 are mainly to be traced back to a change in geometry in the radical cation $H_2O^{\oplus}$[46]. As may be easily seen, PE spectra provide a great deal of information about electron pairs in molecules. The aim of the following section will be to demonstrate the applica-

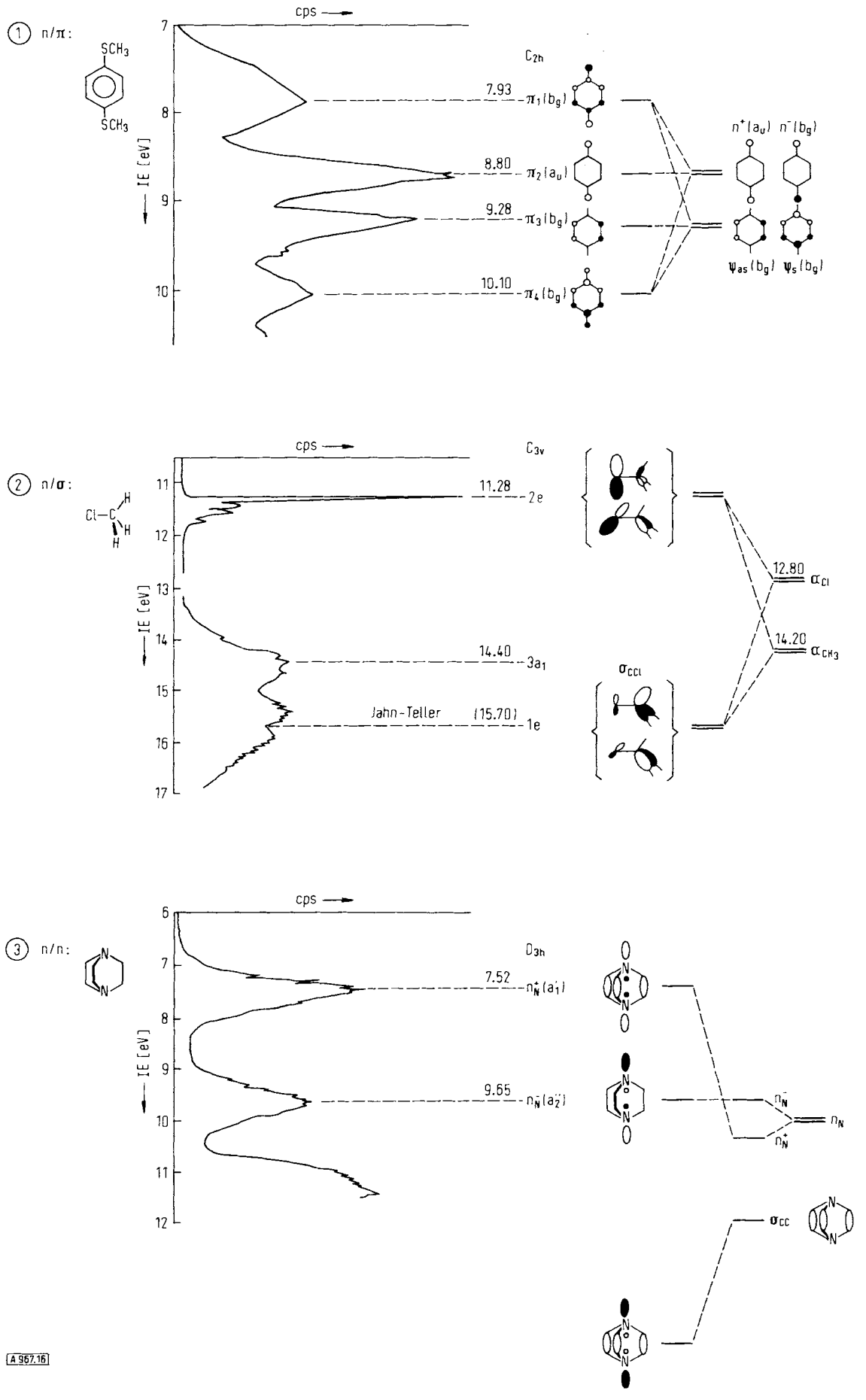


Fig. 16. PE spectra of 1,4-bis(methylthio)benzene [50] methyl chloride [20], and 1,4-diazabicyclo[2.2.2]octane and their assignment with n-π, n-σ, and n-n interaction models.

bility of the MO models introduced in Sections 2 and 3 to the assignment of PE spectra.

4.2. n-π, n-σ, and n-n Interactions

In the interpretation of PE spectra it shows that, "the term 'lone pair' frequently loses much of its meaning and electron pairs in keeping with modern social trends also prefer to live in a commune rather than pairwise isolation"[49]. In an MO picture this means that usually orbitals of the same symmetry type are present which are capable of interactions. In spite of the given general case it is helpful to distinguish between n-π, n-σ, and n-n interactions.

n-π ineractions:

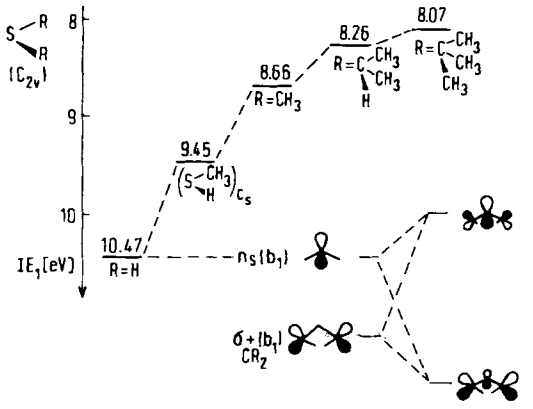
The PE spectrum ①[50] in Figure 16 shows a clearly recognizable n-π splitting. The two sulfur electron pairs can be formally subdivided into the through space combinations $n_S^+(C_{2h}:a_u)$ and $n_S^-(b_g)$, of which only the latter splits with the symmetry-correct $\psi_s(b_g)$ orbital of the 1,4-disubstituted benzene. By contrast $\psi_{as}(b_g)$, although of the same symmetry, cannot mix because of the nodal plane through the substitution centers. (According to the local D_{2h} symmetry which ignores the CH_3 groups ψ_{as} and ψ_s have *different* symmetry assignments.) The symmetry-allowed interaction between $n_S^+(a_u)$ and the nodeless third benzene π orbital (Fig. 9: π_1) is negligible because here the relatively poor n_S-π overlap and the orbital energy separation of about 3.5 eV leave the equal π splitting pattern $\pi_2-\pi_1 \approx \pi_4-\pi_3$ undisturbed.

An enumeration of all PE investigations of n-π delocalization would exceed the limitations of this article. In this connection the PE spectra of additional benzene derivatives should be pointed out with n_N[2a,2c,51–53], n_P[52,53], n_O[2a,50,51], or n_{Hal}[2a,2b,50,54] substituents. Other interesting types of compounds with n-π (n-σ and n-n) interactions are carbonyl halides $X_2C{=}O$[55–57] or thiocarbonyl halides[57,58], and the already discussed boron compounds of coordination number 3. Moreover, the differentiation of σ and π ionizations by the useful "perfluoro effect"[2b,54,55] (cf. Fig. 9) is classified under the rubric "n/π".

n-σ interactions:

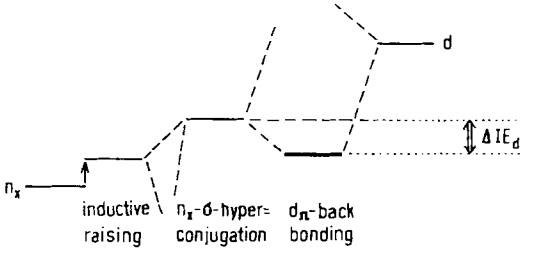
In 1,4-bis(methylthio)benzene, the ionization energy of the sulfur electron pair is lowered by about 1.7 eV relative to H_2S (Fig. 16/①: n_S^+ at 8.8 eV; Fig. 15; n_S at 10.5 eV). An equivalent decrease is found in all other alkyl sulfides[59–61], for example, and can be explained qualitatively by a hyperconjugation model as for the alkyl ethylenes (16).

In simple cases the n-σ interaction may be parametrized with the aid of PE ionization potentials. For the PE spectrum of methyl chloride[2a,62] this may be successfully carried out, analogously to the π-σ splitting in methylacetylene (Fig. 13), with the first ionization potential of hydrogen chloride $IE_1(HCl) = 12.80\,eV$[2a,4] $\equiv -\alpha_{Cl}$ and methane $IE_1(CH_4) = 14.2\,eV \equiv -\alpha_{CH_3}$ (cf. Fig. 13). Insertion into (13) affords the hyperconjugation parameter $\beta_{Cl/CH_3} = -\sqrt{(12.80-11.28)(14.2-11.28)} = -2.1\,eV$. For the PE



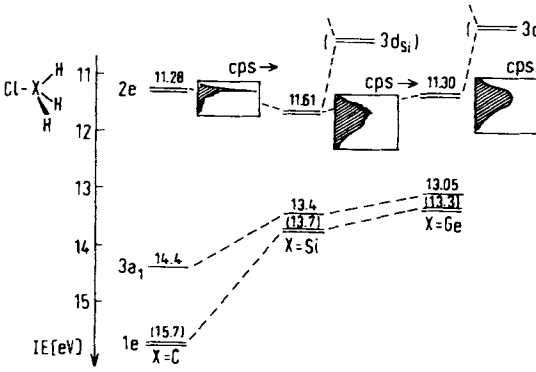
(18)

spectrum of chlorosilane[63,64] whose first band at 11.61 eV is also assigned to the n_{Cl} ionization, a similar parametrization is possible only after an inductive correction of the orbital energies $\alpha_{Cl} \equiv -12.80\,eV$ and $\alpha_{SiH_3} \equiv -12.45\,eV$ (14). A procedure such as this would not take special account of the π back bonding into unoccupied $3d_{Si}$ orbitals although, in analogy with boron ($p_B \overset{\frown}{-} \ddot{n}_X$) π systems, this should also stabilize the two n_{Cl} orbitals (cf. Fig. 7) and could on this basis qualitatively explain the increase of ≈0.3 eV in the n_{Cl} ionization potential compared to CH_3Cl.



(19)

As in the silylacetylenes (14), the overall interaction may be subdivided into individual contributions (19) only in model calculations[40]. The following PE spectroscopic results have been presented to support a significant $(p\text{-}d)_\pi$ contribution to the delocalization of the chlorine electron lone pairs in H_3SiCl. Only the orbitals σ_{XCl} ($3a_1$), σ_{XH_3} (1e) are monotonically raised with decreasing atomic p ionization potentials C (11.3 eV) > Si (8.15 eV) > Ge (7.88 eV), whereas n_{Cl} (2e) goes through a minimum at H_3SiCl.

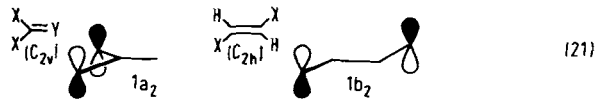


(20)

Moreover, the first PE band in the silyl and germyl derivatives is strongly broadened[63] and shows a smaller spin

orbit coupling[63] in the bromide H_3XBr, and iodide derivatives H_3X—I (cf. Section 4.3); both are evaluated as evidence of stronger electron pair delocalization than in the methyl halides[39,63]. MO models including d orbitals are also useful in the PE spectral comparison of other compounds of the elements X = C, Si, Ge. They provide a qualitative explanation of why, in all the molecules Ë $(XH_3)_n$ where Ë = O[65,66], S[65,67], Se[65], Te[65], N[68,69], As[68], the silicon derivative always exhibits the highest n_E-ionization potential (cf. (20)), and they can be parametrized, *e.g.*, for chlorosilanes H_nSiCl_{4-n}[64,70].

According to the MO definition given in Section 4.1, a delocalization of lone pair electrons n_X is always possible if other orbitals of the same symmetry type are available. For some molecules with lone pair electrons there is nevertheless only one occupied orbital of a given symmetry type which can serve in this case as an internal standard for spectral comparisons, for example[58,64,71,72].



(21)

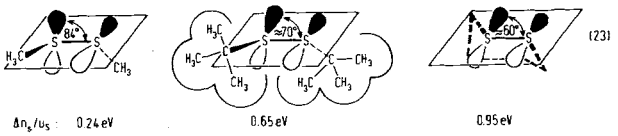
n-n interactions:

The third prototype of electron pair delocalization, with only a few exceptions predicted, is only to be observed together with n-σ interactions, (cf. Section 4.3). The first[73], predicted[74] but nevertheless surprising and therefore often quoted[2b,2c,27,105], PE spectroscopic result is the n-n splitting in 1,4-diazabicyclo[2.2.2]octane (Fig. 16/③). A detailed analysis of the vibrational fine structure exhibited supports assignment of the two first ionizations of the D_{3h} molecule to the orbital sequence $n_N^+(a_1')$, $n_N^-(a_2'')$,... This reversal of the through space splitting n_N^-/n_N^+ depends on the result that the n_N^+ orbital is raised above the n_N^- orbital through antibonding mixing with a $\sigma_{CC}(a_1')$ orbital[75].

Heilbronner and his Basel group have described numerous other n_X-n_X interactions[76-79]:

Obviously, all lone pair electron combinations are more or less mixed with σ orbitals. In each case, the antibonding σ portion determines the orbital sequence n^-/n^+ or n^+/n^- as well as their energy separation, as is especially demonstrated by a comparison of 1,3-cyclobutanedione and *p*-benzoquinone.

In nonplanar systems the n-n splitting increases with decreasing dihedral angle, i. e. with increasing overlap—in the dialkyl sulfides as a result of steric hindrance by bulky groups such as *tert*-butyl, in systems such as 1,2-dithiane[58,61] by ring fixation—and should reach as much as 2.6 eV in coplanar geometries such as five-membered rings.



(23)

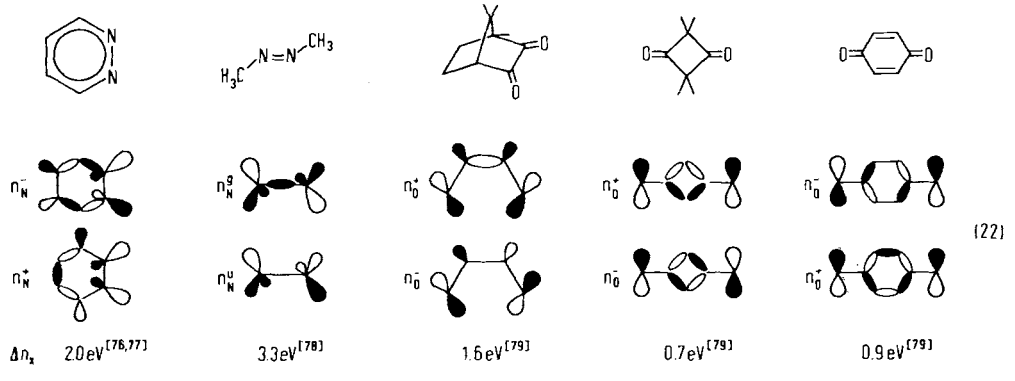
From the numerous PE investigations on molecules with several electron pairs the following random selection is representative: X_2SO[80a], X_2SO_2[80b], $E(Hal)_3$[52,81], $E(Hal)_4$[82], P_4[83], F_3NO[84], $(Hal)_3PO$[84], F_nSN[85], F_2O, Cl_2O[86], $FClO_3$[87], SF_6[81a], ClF_n, BrF_n[88], or XeF_n[89].

The previous resolution of n-π, n-σ, and n-n interactions, for each of which a characteristic PE spectrum is shown in Figure 16, can be described with the qualitative MO models introduced in Sections 3.1 to 3.3. According to the molecular skeleton and bonding partners, various antibonding—or in the case of low-lying electron pairs bonding[70] portions of equal symmetry orbitals result, and thus the broad range of electron "lone" pair ionization potentials of the individual elements can be understood.

4.3. Spin-Orbit Coupling of Electron Pairs

In PE spectra such as that of HBr (Fig. 3) the electron pair ionization energies are split by a further interaction, the coupling between orbital and electron spin angular momentum[*]. This coupling is neglected not only in simple

[*] The degeneracy of radical cation states, which are characterized by ionization of electrons from degenerate orbitals (orbital angular momentum ⩾ 1), is often removed in molecules with heavy atoms through spin-orbit coupling. The states of atoms are designated with the symbol $^{2S+1}\Gamma_J$ in which *S* gives the total electron spin (for radical cations $S = 1/2$), Γ the orbital angular momentum *L* ($S=0$, $P=1$, $D=2$...) and *J* the total value which may assume values from $L+S$, $L+S-1$,... to $L-S$. In molecules Γ is replaced with a corresponding symmetry representation in which symbols such as $^2\Pi_{3/2}$, $^2\Sigma_{1/2}$ ... for linear, or $^2A_{1/2}$, $^2E_{3/2}$, ... for nonlinear molecules appear. (Cf. textbooks such as *J. N. Murrel, S. F. A. Kettle*, and *J. M. Tedder*: Valence Theory. Wiley, London 1965.)

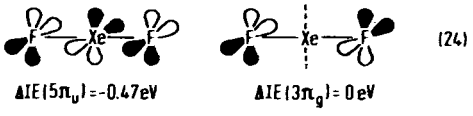


(22)

MO models, but also in most SCF calculations. On the other hand, since it is an important assignment aid in the PE spectra of molecules with heavy atoms, a few rules will be given here which make it easier to deal with spin orbit coupling effects:

a) The spin-orbit splitting increases with increasing atomic number of the atom, for example $Ar^{\oplus}$ (0.178 eV), $Kr^{\oplus}$ (0.665 eV), $Xe^{\oplus}$ (1.306 eV)[2a, 2b], or in molecules[**] for example $CH_3Br^{\oplus}$ (0.32 eV), $CH_3I^{\oplus}$ (0.62 eV)[2, 2b, 90].

b) Spin-orbit coupling can only be observed if a heavy-atom coefficient c_{ju} is included in the MO. Thus splitting is observed in the xenon difluoride $\pi_{u(1/2,3/2)}$ but not in the $\pi_{g(1/2,3/2)}$ orbital which has a node through the central xenon as shown schematically.



(24)

c) In molecules the spin-orbit coupling increases with the electron density ($c_{ju}^2 \times e$) at the heavy atom center. Thus in the PE spectrum of diiodoacetylene, I—C≡C—I, the following differences $\Delta IE(^2\pi_{3/2} - {}^2\pi_{1/2})$ are found[91]: $\Delta IE_1 = -0.44$, $\Delta IE_2 = -0.60$, and $\Delta IE_3 = -0.21$ eV.

d) Degenerate electron pairs are a requirement for strong spin-orbit coupling. Therefore, this splitting component is smaller the more the degeneracy is removed, for example, by n-π interaction. This can be illustrated in an orbital-correlation diagram[90] with increasing interaction parameter $\beta_{n/\varphi}$ ($\varphi = \pi$ or σ) as follows:

In general, spin-orbit coupling effects in molecules can be divided into first order effects, which cause the splitting of degenerate orbitals, and into second order smaller contributions.

In closing, the PE spectrum of iodine[93] will be discussed[94] (Fig. 17), which shows two different spin-orbit couplings, $\Delta IE(^2\pi_{g(3/2,1/2)}) = -0.63$ eV and $\Delta IE(^2\pi_{u(3/2,1/2)}) = -0.79$, although I_2 has the symmetry $D_{\infty h}$. The usual symmetry classification is not sufficient here to characterize the spin molecular orbitals of the iodine molecule. The symmetry group $D_{\infty h}$ can however be extended in a simple way to the douple group $D'_{\infty h}$[95] according to which the orbitals $\pi_{u(1/2)}$ and σ_u belong to the symmetry type $e_{1/2u}$ and the orbitals $\pi_{g(1/2)}$ and $3\sigma_g$ to $e_{1/2g}$. Then the symmetry-allowed mixing of σ character into $\pi_{g(1/2)}$ and $\pi_{u(1/2)}$ orbitals decreases $\Delta\pi_g$ and increases $\Delta\pi_u$ in complete agreement with the iodine PE spectrum.

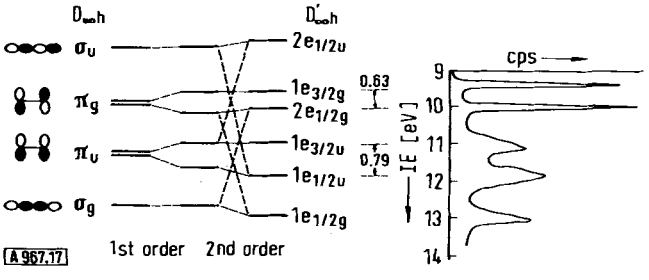
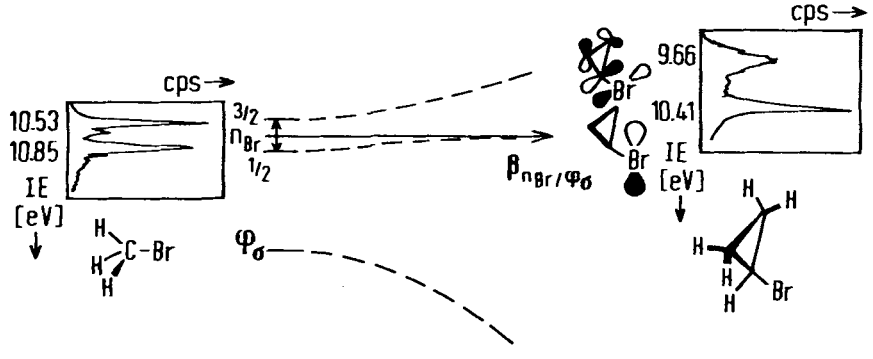


Fig. 17. PE spectrum of I_2 [93] and its interpretation with spin molecular orbitals. ($D'_{\infty h}$)



(25)

One can see from the PE spectral sections of methyl bromide and cyclopropyl bromide how the hyperconjugation interaction of a bromine electron pair with one of the degenerate cyclopropyl Walsh orbitals[2a] makes itself felt. The two n_{Br} ionization potentials are not only lowered and their difference increased[92], but the first PE band broadens[90].

This procedure demonstrated for the iodine molecule has the advantage that the spin orbit coupling is included from the beginning and need not be introduced later as a perturbation. With this useful qualitative approach, PE spectra of more complex molecules such as BI_3 can also be assigned[96].

A broad excursion through PE spectroscopy has thus led from the molecule HBr (Fig. 3) to another diatomic molecule I_2 (Fig. 17). The qualitative MO models useful for interpretation of the spectra have been developed step by step. They can be supported by SCF calculations, and therefore permit, *via* Koopmans' theorem, a simple description of the energy differences between the ground state and the radical cation states of molecules.

[**] The spin-orbit coupling in molecules through heavy atoms is always of the same order of magnitude although smaller than in the atoms themselves. Thus in the free atom the iodine 5p electrons exhibit a spin orbit coupling of 0.942 eV. In the $CH_3I^{\oplus}$ cation, in which one p_I orbital is engaged in the C—I bond, the splitting reduces to about 0.62 eV, *i.e.* 2/3 of the amount 0.942 eV. The ratio of band intensities is at the same time reduced from $^2P_{3/2} : {}^2P_{1/2} = 2:1$ in the atom to $^2\Pi_{3/2} : {}^2\Pi_{1/2} = 1:1$ in the molecule (Fig. 3).

5. Concluding Remarks

In the ten years since the construction of the early UV photoelectron spectrometers, largely by *Turner* and his coworkers[2a], the PE spectra of numerous molecules have been published. The examples selected here should illustrate for the nonspecialist the applicability of the method and the interpretation of the experimental information with MO models. In particular cases, the complete spectral assignment is not always so easy to make and so certain as the deliberately simplified MO considerations might suggest.

The flood of individual PE data may be organized under an overall point of view by qualitative MO models[19,27,31], whose utility stretches from the Hückel $(4n+2)$ rule to Woodward-Hoffmann orbital symmetry correlations. The fundamental simple concepts of symmetry, overlap, energy gap, and of orbital perturbation, which have been derived out of the comparison of chemical experience and theoretical calculations, may be successfully carried over into the discussion of photoelectron spectra and thus are reconfirmed.

The apparent common validity of Koopmans' theorem is a requirement of the close relationship between PE spectroscopy and MO theories. Known exceptions[2b,3] mostly depend on strong electrostatic interactions and electron reorganization in the radical cation, for example in easily polarizable parts of the molecule. These exceptions and also other aspects such as the relationship of PE to Rydberg states of molecules[97-99], can all serve as a starting point for theoreticians.

In contrast, the chemist will ask what help the information from a PE spectrum can give him. The following answers may be given: our knowledge of molecules is broadened, especially concerning their σ skeletons which were up to now only poorly accessible to measurement. PE ionization energies can also be correlated with numerous other physical measurement data such as half wave oxidation potentials[100], charge transfer ionization energies[50,59], pK values[77,101], or electronic transition energies[97-99,102]. Occasionally structural aspects in molecules may be elucidated[80a,103-105] and some analytical applications have been investigated[106]. Above all, however, the more general observations derived from PE spectral assignments, for example concerning substituent effects or chemically related compounds, will help the chemist in his own work.

The MO models employed in interpretation of PE spectra are useful to explain further molecular properties and in this way create overall order in a collection of otherwise solitary facts: Herein—the simple construction of the PE spectrometer will prevent its simply becoming a "black box"—lies at the same time the educational utility of PE spectroscopic arguments in the teaching of general chemistry.

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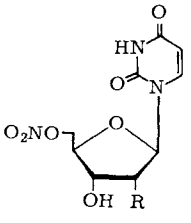
COMMUNICATIONS

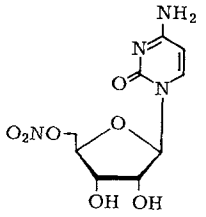
5′-Nitrates of Pyrimidine Nucleosides: Nitric Acid Analogs of Nucleotides[1][**]

By *F. W. Lichtenthaler* and *H. J. Müller*[*]

Depending upon the experimental conditions the direct reaction of unprotected pyrimidine nucleosides with nitric acid can lead to nitration at C-5 of the nucleobase accompanied by oxidation of the 5′-hydroxyl group to carboxyl[2] or to formation of nitrates from the sugar-hydroxyl groups, the latter leading to di-*O*- and tri-*O*-nitro nucleosides[3,4]. We here describe conditions that permit 5′-*O*-nitro nucleosides (nucleoside 5′-nitrates), *e.g. (1)* to *(3)*, to be obtained in preparatively useful yields directly from ribo- and deoxyribo-nucleosides[5]. As nitrate analogs of the 5′-phosphates these products warrant pharmacological interest.



(1), R = OH
(2), R = H



(3)

For example, treatment of uridine with 90% nitric acid (1.5 h, −70 °C) affords a mixture of 5′-*O*-nitrouridine *(1)*, two di-*O*-nitro compounds in the ratio 5:1, and about 40% of unchanged starting material. Extraction of this mixture with ethyl acetate gives a 44% yield of *(1)* as needles of m. p. 139 °C and $[\alpha]_D^{20} = +16°$[6], whereas from the di-*O*-nitro fraction so far only a 5% yield of pure 3′,5′-di-*O*-nitrouridine has been isolated (layer chromatography; platelets of m. p. 179—182 °C, $[\alpha]_D^{20} = +12°$).

Applying the above conditions to 2′-deoxyuridine affords the 5′-*O*-nitro derivative *(2)*, m. p. 175 °C, $[\alpha]_D^{20} = +42°$, in 20% yield with 13% of 3′,5′-di-*O*-nitro-2′-deoxyuridine, m. p. 113 °C (129 °C[3]), $[\alpha]_D^{20} = +12°$. From cytidine under the same conditions there is formed a 5:1 mixture of the 5′-*O*-nitro compound *(3)* and two dinitro derivatives, from which *(3)* can be separated in 46% yield as needles of m. p. 160—161 °C, $[\alpha]_D^{20} = +28°$.

That the products are 5′-*O*-nitro compounds follows unambiguously from the NMR spectroscopic data of *(1)*—*(3)*, in particular from the position of the 5′-CH_2 signal which is shifted paramagnetically by about 1.2 ppm from that in the starting materials.

No problem should arise in applying this process of direct 5′-*O*-nitration to preparation of further 5′-*O*-nitro derivatives of pyrimidine nucleosides.

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5'-O-Nitrouridine (1)

Uridine (1.2 g, 4.9 mmol) is added with vigorous stirring to 90% nitric acid ($\rho = 1.48$; 7.5 ml) precooled to $-70\,^{\circ}C$. The solution, which soon becomes clear, is stirred for 1 h at $-70\,^{\circ}C$ and after addition of further 90% HNO_3 (7.5 ml) for a further 30 min at $-70\,^{\circ}C$[7]. The mixture is then stirred into ice-water (80 ml), covered with a layer of ethyl acetate (50 ml), and neutralized by portionwise addition of solid $NaHCO_3$. The aqueous phase[8] is extracted with ethyl acetate (6 × 50 ml), and the combined extracts are dried ($MgSO_4$) and evaporated. When the residual foam is taken up in hot ethanol, treated with charcoal, and slowly cooled, the ester *(1)* crystallizes as colorless needles of m.p. 139 °C, $[\alpha]_D^{20} = +16^{\circ}$ ($c = 1$, DMF).

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[6] All the new compounds described gave satisfactory analytical data on combustion. Rotations were all determined for *N,N*-dimethylformamide solutions at $c = 1$.

[7] Vigorous stirring is essential to prevent the mixture from solidifying.

[8] The organic phase contains the mononitrate *(1)* and dinitrate in the approximate proportion 1:1 (TLC in $CHCl_3/CH_3OH$ 9:1); separation by preparative layer chromatography (20 × 40 cm plates with 1.75 mm of Merck silica gel $PF_{354+366}$ and 9:1 $CHCl_3$/methanol as eluant) affords a further 100 mg (7%) of *(1)*.

How "Aromatic" are λ⁵-Phosphorins? Electrophilic Substitution Reactions

By *Werner Schäfer* and *Karl Dimroth*[*]

Dedicated to Professor Karl Winnacker on the occasion of this 70th birthday

"Aromaticity"[1] from the standpoint of preparative organic chemistry characterizes the chemical behavior of compounds like benzene where *substitution* of an H atom by another group with retention of the unsaturated system is preferred over *addition* leading to a more saturated system. On treatment of phosphonium ylides with electrophiles a two-step reaction is always observed: addition to the phosphonium salt and, if a sufficiently strong base is present, loss of a proton. If the new, substituted ylide is sufficiently stabilized by mesomerism, the proton can also be transferred to the less stabilized initial ylide, a mechanistic sequence which is called "transylidation"[2].

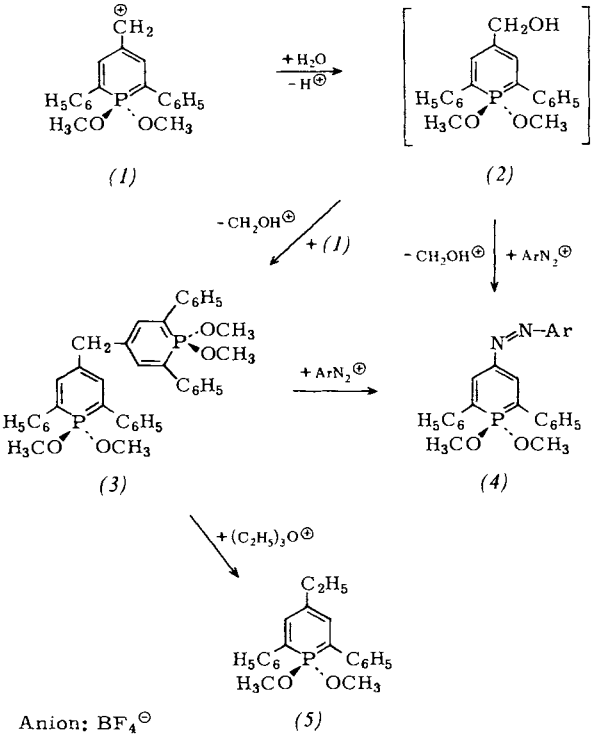
Reactions of this kind were also observed by *Märkl et al.* on treatment of cyclic 6π-delocalized phosphonium ylides such as 1,1-diphenyl- and 1,1,2-triphenyl-phosphanaphthalene[3]. With methyl iodide or diazonium salts the first products are phosphonium salts which can be converted into 4- or 2-substituted 1,1-diphenyl-λ⁵-phosphanaphthalenes by bases; on reaction with acid chlorides these products were formed directly by transylidation.

Since other concepts of aromaticity suggest that 1,1-dialkoxy-λ⁵-phosphorins[4] are considerably more "aromatic" than 1,1-dialkyl or 1,1-diaryl-λ⁵-phosphorins[1,2], these very weakly basic compounds ought to be suitable for electrophilic aromatic substitutions at C-2 or C-4. Experimental tests of this deduction have, however, been impossible since 1,1-dialkoxy-λ⁵-phosphorins with a replaceable H atom on C-2 or C-4 have hitherto been inaccessible.

In an earlier communication we reported the synthesis of λ⁵-phosphorins containing electrofugal groups other than a proton on C-4[6]. We are now able to show that these derivatives can be electrophilically substituted, smoothly and in high yield, even in acidic media, without any evidence of a phosphonium salt as intermediate.

One of these λ⁵-phosphorins is (1,1-dimethoxy-2,6-diphenyl-λ⁵-phosphorin-4-yl)carbenium tetrafluoroborate *(1)*[5]. In acetonitrile containing a little water it first produces the alcohol *(2)*, which immediately undergoes electrophilic substitution, losing formaldehyde cation, by *(1)* still present in the solution to give *(3)*[6] or by aryldiazonium tetrafluoroborates to give *(4)*.

(3) also contains a good electrofugal group. It reacts with diazonium salts, giving *(4)*, and the yields of *(4)* in the presence of water are almost quantitative by the route *(1)* → *(2)* shown. In another electrophilic substitution *(3)* can be alkylated by triethyloxonium salts to give 4-ethyl-1,1-dimethoxy-2,6-diphenyl-λ⁵-phosphorin *(5)*, which is also accessible by another route[7]. Treatment of *(3)* with triphenylcarbenium tetrafluoroborate *(6)*



(1) (2) (3) (4) (5)

Ar	*(4)*, m.p. [°C]	*(11)*, m.p. [°C]
p-$CH_3C_6H_4$	186—188	210—211
p-$CH_3OC_6H_4$	153—156	194
2-CH_3—4-$NO_2C_6H_3$	181—183	247—250

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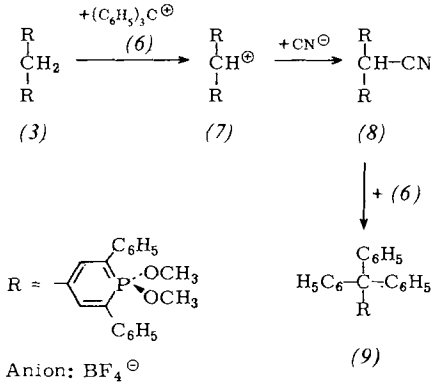
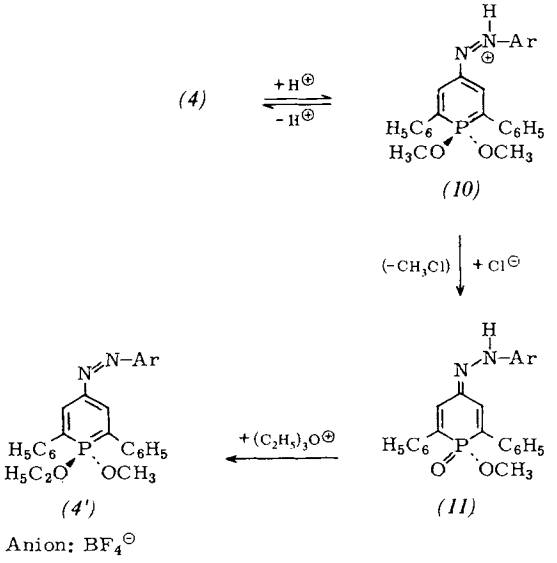
forms only bis(1,1-dimethoxy-2,6-diphenyl-λ^5-phosphorin-4-yl)carbenium tetrafluoroborate *(7)* by hydride transfer. However, the nitrile *(8)*, readily obtained by addition of cyanide to *(7)*, reacts smoothly with *(6)* in an electrophilic substitution yielding 1,1-dimethoxy-2,6-diphenyl-4-trityl-λ^5-phosphorin *(9)*, m. p. 144—145 °C.



Electrophilic substitution with removal of the cation of formaldehyde or benzaldehyde instead of a proton has long been known in the benzene series[8]. This reaction has been used to synthesize aldehydes starting from suitably *C*-substituted derivatives of *N*,*N*-dimethylaniline[9]. The high π-electron density at position 4 of the above λ^5-phosphorin derivatives is in full accord with theoretical calculations[10] and photoelectron spectroscopy[11]. The complete analogy of the reactions described with those of corresponding derivatives of *N*,*N*-dimethylaniline thus underlines the typical "aromatic" electron-rich character of 1,1-dialkoxy-λ^5-phosphorins[12].

The azo compounds *(4)* are protonated by acid, not on the nucleus (C-4) to give phosphonium salts, but on the β-N atom to give *(10)*. Deprotonation by ethyldiisopropylamine regenerates *(4)*.



Reaction with acids containing easily polarizable anions, *e.g.* HCl, yields, irreversibly, with loss of methyl chloride, the phosphinic acid derivatives *(11)*. These can be transformed back into azo compounds *(4')* by alkylation with triethyloxonium tetrafluoroborate in the presence of ethyldiisopropylamine[13].

Elemental analyses, mass spectra and NMR, IR, and UV spectra of all the new compounds accord with the formulas assigned.

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Ligand Influences in Heterogeneous Catalysis: Modification of the Phillips Catalyst[**]

By *G. Henrici-Olivé* and *S. Olivé*[*]

Catalyst tailoring by a systematic variation of the ligands seems to be on its way to becoming a powerful tool in homogeneous catalysis on transition metal centers[1]. It appears opportune to apply the same principles to heterogeneous catalysts. We reported recently on the influence of titanium containing ligands on molybdenum oxide catalysts for the metathesis of olefins[2]. The present communication deals with the modification of the heterogeneous catalyst for the polymerization of ethylene, based on SiO_2-supported chromium oxide (Phillips catalyst), and its interpretation in terms of ligand influences.

The molecular weight of polymer in this type of catalysis depends on the relative rates of chain propagation (rate constant k_p) and chain transfer (β-hydrogen transfer; rate constant k_{tr}):

$$Cr\text{–}(P)_n + CH_2{=}CH_2 \xrightarrow{k_p} Cr\text{–}(P)_{n+1}$$

$$Cr\text{–}CH_2\text{–}CH_2\text{–}(P) \xrightarrow{k_{tr}} CrH + CH_2{=}CH\text{–}(P)$$

$(P)_n$ stands for a polyethylene chain of n monomer units.

The latter reaction is enhanced by increasing the electron affinity of the metal center[3], and can in principle be controlled by choosing the proper ligands.

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[**] We recognize valuable experimental help from Miss *E. Arnold* and Mr. *H. Kull*.

There is good evidence that Cr^{II} is the active valence state in heterogeneous[4] and homogeneous[5] chromium catalysts. In this oxidation state the chromium center possesses poor acidity (high molecular weight polymer). In homogeneous Cr systems, a certain degree of control of the molecular weight has been achieved varying the acidity of the alkylaluminum in the active species[5]. Translating this knowledge to the heterogeneous Cr catalyst, highly acidic ligands are required if the aim is to lower the degree of polymerization. Because of the severe conditions of activation and regeneration of the supported catalysts, only metal oxides can be considered as additives: ZnO, WO_3, and MoO_3—in order of increasing activity—were found to be effective (Table 1).

The catalysts were prepared by impregnating SiO_2 (spheres of 0.2—0.5 mm diameter) with aqueous solutions of CrO_3 and/or ammonium molybdate. After removal of excess liquid, the catalysts were dried and oxidized at 500 °C in an O_2 stream. Before use they were activated with CO (500 °C, 3 h). A pyrex tube of 60 cm length and 2 cm diameter was used as reactor.

Table 1. Influence of molybdenum additive on SiO_2-supported chromium oxide catalyst. Substrate: ethylene; $T=300$ °C; $[Cr]=1\times10^{-3}$ g-atom/g catalyst.

v [a]	Mo/Cr	Conversion [%]	Product distribution [%]				
			C_3	C_4	C_5	C_6	Polymer + cracked products
0.65	0	54.7	—	4.4	—	0.5	95.1
	1	25.8	57.3	31.4	6.6	4.7	—
	3	22.0	75.0	20.0	3.6	1.4	—
1.3	0	56.3	—	6.6	—	1.0	92.4
	1	21.5	49.8	37.2	7.0	6.0	—
	3	18.7	75.9	18.2	4.3	1.6	—

[a] Flow rate [mol ethylene/(min × g-atom Cr)].

Table 1 shows that the modification of the chromium catalyst has a considerable influence on the molecular weight of the product. In the absence of Mo, high polymer is formed which, for the most part, is cracked under the present conditions, to give highly branched, liquid oligomers of a molecular weight of about 250—300, with poor unsaturation. Addition of the Mo species, on the other hand, converts the Phillips catalyst into an oligomerization catalyst. The growing chains leave the catalytic center after two to three propagation steps, as butene or hexene. Only traces of octene and no higher oligomers are detected. The data show also that the molybdenum additive has a dual function, not only drastically decreasing the chain length, but also operating as a metathesis catalyst. By this latter action, oligomers with odd carbon numbers are formed, particularly C_3, the amount increasing with increasing ratio Mo/Cr.

At lower temperatures and/or lower flow rate, the modified catalysts give some polymer and cracked material besides the oligomer. The same is true at $Mo/Cr<1$. It should also be noted that MoO_3 alone, on SiO_2, is practically inactive (≤ 0.3 % conversion to butene under the conditions given in Table 1).

Magnetic measurements give some information concerning the active species. The magnetic moments, calculated from magnetic susceptibility data, are given in Table 2. Numbers in the same line refer to different catalyst preparations (oxidation-reduction cycle), and indicate the reproducibility of these data. MoO_3 alone is only partially reduced with the present treatment (30—50 % reduction to Mo^V, one unpaired electron). In the presence of chromium, the reduction appears to be much less, since the magnetic moment found for the "bimetallic" catalyst is essentially the same as that for the chromium catalyst alone.

Table 2. Magnetic moments of metal oxide catalysts. $[Cr]=[Mo]=1\times10^{-3}$ g-atom/g catalyst; $T=21$ °C; reduction: 3 h, 500 °C, CO.

Metal oxide	μ_{eff} [μ_B]	
Cr	3.92	3.97
Mo	1.03	1.27
Cr + Mo [a]	3.92	4.08

[a] Calculated for Cr.

A paramagnetic Mo species may be observed by EPR, in the bimetallic system as well as in the Mo system alone (Fig. 1). The Cr catalyst presents a weak signal, presumably due to traces of Cr^{III}; it remains unchanged in the spectrum of the bimetallic catalyst. (Cr^{II} is not expected to give a signal at room temperature.)

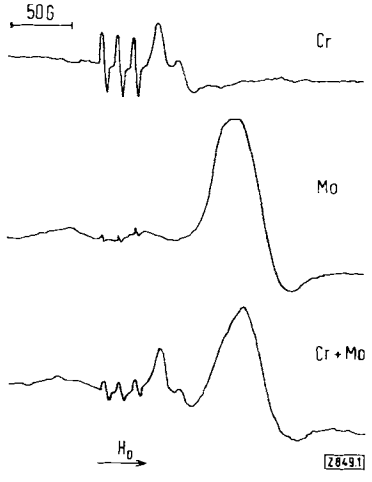
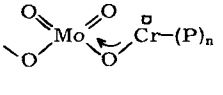


Fig. 1. EPR signals of SiO_2-supported catalysts after CO treatment. $T=20$ °C; field marker: Fremy's salt.

The signal of the pure Mo system clearly differs in line shape from that of the Mo peak of the bimetallic catalyst. We interpret this as evidence for an interaction between the two metals. Although only the reduced molybdenum gives an EPR signal, it is reasonable to assume a comparable interaction also for Mo^{VI}.

Our knowledge concerning the active species may be summarized as follows: It contains chromium as Cr^{II}, and molybdenum predominantly as Mo^{VI}; there is interaction between the two metals; best results are obtained when [Mo]/[Cr] is near unity. With these data, the following structure may be suggested:



where □ represents a vacancy in the coordination sphere of the chromium, available for coordination of the olefin. The withdrawal of electron density from the Cr center by the acidic molybdenum oxide is assumed to be responsible not only for the drastic reduction of the molecular weight of the product, but also for the diminution of

the overall rate (cf. Table 1). This latter influence, which is a consequence of a relative stabilization of the metal-carbon bond, is also known from homogeneous catalysis[3, 5].

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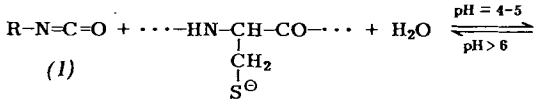
Methoxymethyl Isocyanate as a New Agent for Reversible Protection of SH Groups in Protein and Peptide Chemistry

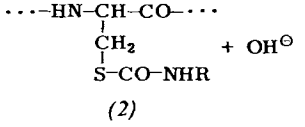
By *Harald Tschesche* and *Helmut Jering*[*]

The usual blocking reagents for use during alkylation, mercuration or oxidation of the SH group of cysteine[1] lead to irreversible formation of the derivative of the thiol group.

We have found that methoxymethyl isocyanate *(1a)* is excellently suited for rapid and selective carbamoylation of cysteine-SH at pH 4—5 in an aqueous medium and at room temperature. The reaction yielding *(2a)* occurs very fast and is complete in less than 2 min when an excess of the reagent is used. The α- and ε-amino groups do not react under the stated conditions. The *N*-methoxymethyl-*S*-carbamoyl derivative *(2a)* of cysteine is sufficiently stable at pH 6 (see Table 1). For comparison it should be noted that the half-life of the unsubstituted *S*-carbamoyl derivative *(2b)* from cyanate and cysteine is only about 10 min at 25 °C and pH 6[2].



(1)



(2)

(a), R = $H_3C-O-CH_2$; *(b)*, R = H

Methyl, ethyl, and *tert*-butyl isocyanate react only very slowly at pH 4—7 in an aqueous medium and are thus barely useful for our purpose.

Unblocking of the SH group with removal of the *N*-methoxymethyl-*S*-carbamoyl protecting group is easily achieved under mild conditions in an aqueous alkaline medium (see Table 1): at pH 9.6 its removal from cysteine is complete in 30 min and from glutathione in 60 min.

We have used methoxymethyl isocyanate *(1a)* as protecting group for reversible blocking of the SH group in cysteine, glutathione, papain and for the trypsin-kallicrein inhibitor from bovine organs after its selective reduction at Cys^{14}-Cys^{38}[3].

Table 1. Removal of the protecting group from cysteine (Cys) or glutathione (GSH) at room temperature.

pH	*t* [min]	Liberation of SH [%] Cys	GSH
9.6	30	100	80
8.6	100	100	55
7.6	100	67	20
6.0	180	2	1.5

The enzymatic activity of papain was instantaneously blocked by reaction of methoxymethyl isocyanate with the reactive thiol group of Cys^{25}. The proteolytic activity of the enzyme deactivated at pH 5.6 was restored by incubation at pH 8.8 and 20 °C within 60 min to 50%.

When the trypsin-kallicrein inhibitor from bovine organs has been selectively reduced by sodium tetrahydridoborate, the two SH groups formed from the disulfide bridge[3] react quantitatively with *(1a)* under the conditions described, and the two-fold *S*-carbamoylated inhibitor is completely inactive against trypsin. Removal of the SH-protecting groups at pH 9.5 and 20 °C in the presence of glycylglycine with subsequent oxidation of the neighboring thiol groups to the disulfide bridge by access of oxygen at the same pH regenerates the activity of the inhibitor completely within 60 min.

General experimental directions:

1 μmol of the peptide or protein is dissolved in 0.5 ml of 0.2 M sodium succinate buffer (pH 4.0, papain at pH 5.6), and for each mol of cysteine 350 μmol (for papain 20 μmol only) of methoxymethyl isocyanate *(1a)*[4], dissolved in dimethylformamide [50 μl of *(1a)* in 150 μl of DMF], is added with stirring at room temperature. Quantitative reaction occurs within 2 min with simultaneous mild evolution of CO_2. The mixture is stirred for a further 3 min for complete destruction of the reagent, and the solution is then subjected to gel filtration on Sephadex G-15 or Bio Gel P-2 in 10% acetic acid so as to separate the products and buffer salts. The *N*-methoxymethyl-*S*-carbamoyl derivative *(2a)* can be preserved in acid solution or lyophilized from acid solution. Disulfide bridges reduced under nitrogen by $NaBH_4$ can be treated with *(1a)* directly in the reaction mixture after buffering at pH 4 for removal of the acid used to destroy the excess of reducing agent.

For removal of the SH-protecting group, 1 μmol of the protected peptide or protein is dissolved in 0.5 ml of 0.1 M tris/HCl buffer (pH 9.5), 1 mg of glycylglycine is added as cyanate trap, and the solution is set aside at room temperature for 60 min. To avoid undesired reoxidation of the SH groups this removal is carried out under nitrogen.

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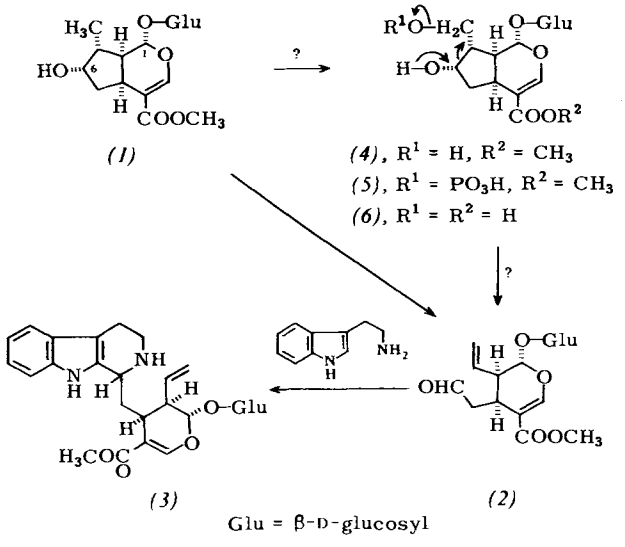
[4] We thank Bayer AG, Leverkusen, for a sample.

Total Synthesis of Hydroxyloganine and Hydroxyloganic Acid[**]

By *Lutz-F. Tietze*[*]

The naturally occurring monoterpene glycosides loganine *(1)* and secologanine *(2)* hold a key position in the biogenesis of *Corynanthe*[1], *Aspidosperma*[1], and *Iboga*[1], as well as *Ipecacuanha*[2] and *Cinchona*[3] alkaloids.

The conversion of loganine *(1)* into secologanine *(2)* occurring *in vivo* involves cleavage of the cyclopentane ring and formation of an aldehyde group which can react by Mannich condensation with biogenetic amines such as tryptamine to yield, from the latter, vincoside *(3)*[4].



(1)

(4), R^1 = H, R^2 = CH_3
(5), R^1 = PO_3H, R^2 = CH_3
(6), R^1 = R^2 = H

(3) *(2)*

Glu = β-D-glucosyl

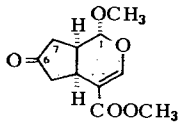
The mechanism of biological cleavage of the carbocyclic ring of *(1)* is not yet known and is difficult to understand without assumption of intermediates.

Numerous analogies are known for cleavage of a compound of hydroxyloganine type *(4)*, which can fragment in its phosphorylated form to yield *(2)* in the manner indicated[5]. Here all the centers concerned are in anticoplanar relation.

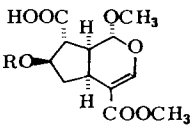
This would make the hitherto unknown hydroxyloganine *(4)* into a key compound in the biosynthetic sequence leading to the alkaloids mentioned above.

The starting material for the total synthesis of hydroxyloganine *(4)* and hydroxyloganic acid *(6)* was the ketone *(7)*, which is accessible by photoaddition of 3-cyclopentenyl 2-tetrahydropyranyl ether and methyl 2,2-diformylacetate[6]. Treatment of *(7)* with magnesium methyl carbonate in dimethylformamide at 135 °C[7] and subsequent reduction by $NaBH_4$ gave the 6-hydroxy carboxylic acid *(8)*, the carboxyl group being introduced at the sterically less hindered C-7.

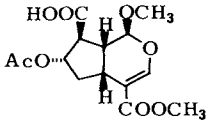
It proved impossible to resolve *(8)* into its antipodes by means of the usual bases. *(8)* was therefore acetylated, giving *(9)* [m.p. 164—165 °C, yield 69% based on *(7)*],



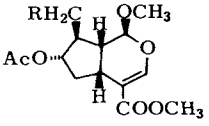
(7), (racemate)



(8), R = H(racemate)
(9), R = Ac(racemate)
(10), R = Ac



(11)

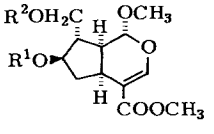


(12), R = OH
(13), R = OMs
(14), R = SC_2H_5
(15), R = H

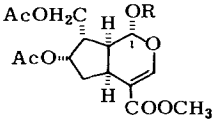
which was resolved with (−)- and (+)-α-methylbenzylamine to *(10)* (m.p. 165—166 °C, $[\alpha]_D^{25} = -68°$) and *(11)* [m.p. 164—165 °C, $[\alpha]_D^{25} = +67°$]. Reduction by diborane in tetrahydrofuran afforded the alcohols *(16)* (m.p. 128—129 °C, $[\alpha]_D^{25} = -75°$) and *(12)* (m.p. 129 to 130 °C, $[\alpha]_D^{25} = +75°$), respectively, in 92% yields.

To prove the stereochemistry assumed, *(12)* was converted successively into the mesylate *(13)*, the thioether *(14)*, and, by selective hydrogenation with Raney nickel, into the (+)-6-*O*-acetyl-1-*O*-methyl-6-epiloganin aglucone *(15)*, whose NMR, IR, and UV spectra and rotatory power agree with those of the (−)-antipode of *(15)* which was prepared from authentic loganine[8].

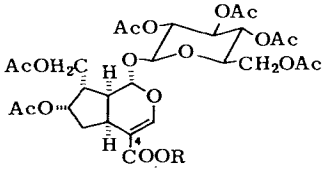
Hydrolysis of *(16)* by barium hydroxide in anhydrous methanol to the diol *(17)*, conversion thereof into the dimesylate *(18)* (m.p. 146 °C; $[\alpha]_D^{25} = -72°$), and exchange of the mesyl groups with epimerization at C-6 by means of tetraethylammonium acetate in acetone gave the diacetate *(19)* in 62% yield (m.p. 97 °C, $[\alpha]_D^{25} = -31°$).



(16), R^1 = Ac, R^2 = H
(17), R^1 = R^2 = H
(18), R^1 = R^2 = Ms



(19), R = CH_3
(20), R = H(+anomer)



(21), R = CH_3
(22), R = H

Cleavage of the acetal group of *(19)* was effected by perchloric acid in aqueous acetic acid, affording a mixture of anomeric semiacetals *(20)* in 84% yield; ^{1}H-NMR data indicate that here the isomer with pseudoaxial configuration of the OH group[9] is formed to the extent of about 90%.

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Glycosidation of the anomeric semiacetals *(2)* with 2,3,4,6-tetra-*O*-acetyl-β-D-glucose and boron trifluoride-ether in dichloroethane[10] and chromatographic separation gave a 6% yield of hydroxyloganine hexaacetate *(21)* [$[\alpha]_D^{25} = -58°$; UV (CH_3OH): $\lambda_{max} = 232$ nm ($\log\varepsilon = 4.01$)]. Deacetylation and hydrolysis of the ester group on C-4 of *(21)* by barium hydroxide in aqueous methanol yielded hydroxyloganic acid *(6)*, which was converted into hydroxyloganine *(4)* [$[\alpha]_D^{20} = -61°$; UV (CH_3OH): $\lambda_{max} = 236$ nm ($\log\varepsilon = 4.02$)] by diazomethane and into hydroxyloganic acid hexaacetate *(22)* [m.p. 158 °C; $[\alpha]_D^{20} = -56°$; UV (CH_3OH): $\lambda_{max} = 234$ nm ($\log\varepsilon = 3.97$)] by acetic anhydride in pyridine.

Treatment of hydroxyloganine *(4)* with acetic anhydride in pyridine and of *(22)* with diazomethane regenerated hydroxyloganine hexaacetate *(21)*.

The identities of the new compounds were confirmed by elemental analyses, ^{1}H-NMR, IR, and UV spectra and high-resolution mass spectra.

Synthesis and feeding of hydroxyloganine specifically labeled by ^{3}H and ^{14}C is currently being carried out in collaboration with Prof. *A. R. Battersby*, Cambridge (England).

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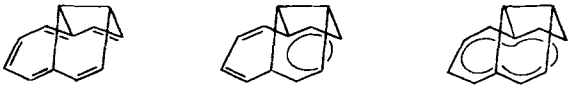
Semibullvalenes as Potential Homoaromatic Compounds

By *Emanuel Vogel*, *Udo H. Brinker*, *Klaus Nachtkamp*, *Jürgen Wassen*, and *Klaus Müllen*[*]

According to EH and MINDO/2 calculations[1], the introduction of suitable substituents into semibullvalene *(1)* may reduce the activation energy of the Cope rearrangement to negative values, so that molecules with homoaromatic properties result[2]. This supposition prompted *Paquette et al.*[3] to discuss the interesting possibility that the semibullvalene *(2)* resulting from bridging *(1)* by a 1,3-butadiene unit—and its valence isomer *(4)*—should exist either as a homoaromatic 6π- or a 10π-electron system [*(5)* and *(6)*, respectively].

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

These authors were able to synthesize a hydrocarbon to which the structure tricyclo[5.4.1.0^{4,12}]dodeca-2,5,7,9,11(1)pentaene *(4)* applied unambiguously. It was not, however, established whether or not *(4)* is in fact homoaromatic.



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

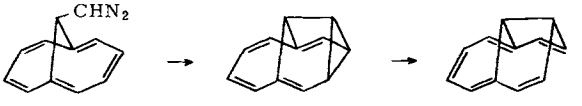
That investigation touched our studies of bridged [14]annulenes[4] in a very delicate way. Thus, if a second 1,3-butadiene unit is fused to *(1)* one arrives at compound *(3)*, a molecule which we recently encountered[5] as its valence isomer *(7)*, *i.e.* 1,6;8,13-ethanediylidene[14]annulene.

(7)

In our assessment the remarkable thermodynamic stability of *(7)* is to be ascribed primarily to the aromatic delocalization of the peripheral 14π-electron system[4, 6]. This view would doubtless require revision if it should be shown that the Paquette hydrocarbon, which is contained as a structural unit in *(7)*, has pronounced homoaromaticity, approximately comparable with that of the homotropylium ion[2] or tricarbonyl(tricyclo[4.3.1.0^{1,6}]deca-2,4-diene)-chromium[7].

We now report an independent synthesis of *(4)* and show by spectroscopic comparisons that the homoaromatic structures *(5)* and *(6)* make no important contribution to the ground state of the molecule.

The starting point of our approach to *(4)* was 1,6-methano[10]annulene-11-carbaldehyde, m. p. 103—104 °C, obtainable in 75% yield from 11-lithio-1,6-methano[10]annulene[8] and dimethylformamide in tetrahydrofuran at −70 °C. With hydrazine hydrate in methanol this aldehyde gave its hydrazone which was not isolated but was subjected directly in ethereal solution to oxidation by silver oxide; the resulting diazo compound *(8)* suffered



(8) *(9)* *(4)*

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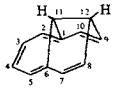
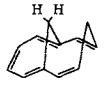
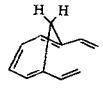
spontaneous decomposition under the reaction conditions to give a mixture of $C_{12}H_{10}$ hydrocarbons[9]. Separation of the mixture on an alumina column impregnated with $AgNO_3$ (20%) (eluant: benzene pentane 1:1) afforded the desired tricyclo[5.4.1.$0^{4,12}$]dodeca-2,5,7,9,11(1)-pentaene *(4)* which was formed by way of *(9)* and was isolated in 5—7% yield as a faintly yellow compound (actual color), extremely sensitive to air, b.p. 37—38 °C/0.02 torr, m.p. 7—8 °C (needles from methanol) [UV spectrum: λ_{max}(cyclohexane) = 245 (ε = 31 500, shoulder), 253 (32300), 338 nm (2800)]. Naphthalene (42%), benzocyclooctatetraene (6%), and 11-methylene-1,6-methano[10]annulene (2%) were obtained in addition to *(4)*.

The NMR spectrum (cf. Table 1) seemed most likely to clarify the homoaromaticity problem connected with *(4)*. If *(4)* exists as the homoaromatic species *(6)*, a diamagnetic ring current is to be expected that should manifest itself in a deshielding of the vinylic protons, in shielding of the bridge proton 11-H[**] complimentary thereto, and presumably also in equalization of the vicinal coupling constants $J_{2,3}$ and $J_{3,4}$.

For evaluation of the NMR spectrum of *(4)* it was deemed necessary to enlist the spectra of suitable model compounds for comparison. A model for a non-delocalized *(4)* seemed to us to be 1,6-divinylcycloheptatriene *(11)*[10] because strong homoconjugation such as is being discussed for *(4)* need not be considered seriously for this conformationally labile molecule. In fact the NMR spectrum of *(11)* accords to a great extent with the spectra of 1,6-alkylated cycloheptatrienes so far as comparisons are possible[11]. 1,6-Methano[10]annulene is a clear reference compound for *(4)* delocalized in the manner of formula *(6)*. For completeness bicyclo[5.4.1]dodeca-2,5,7,9,11-pentaene *(10)*[12], which occupies a position between *(4)* and *(11)*, was included in the discussion (cf. Table 1).

Table 1. ^{1}H-NMR parameters [100 MHz spectra (in CCl_4); τ values in ppm; *J* (in Hz)] of *(4)*, *(10)*, and *(11)*. The numbering of *(4)*, chosen on the basis of analogies, and not corresponding with IUPAC nomenclature, applies also to the hydrocarbons *(10)* and *(11)*.

	 *(4)*	 *(10)*	 *(11)*
τ 3-H, 4-H	3.36	3.26	3.50
τ 2-H, 5-H	3.70	3.71	3.88
τ 7-H, 10-H	3.60	3.72	3.59
τ 8-H, 9-H	4.03	5.22	4.57
			4.96
τ 12-H	6.24	6.21	
		7.02 [b]	
τ 11-H_{syn} [a]	8.24	9.80	
			7.48
τ 11-H_{anti}		6.20	
$J_{2,3}$	6.44	6.02	6.14
$J_{3,4}$	10.99	10.58	11.38
$J_{7,8}$	5.30	11.48	10.57
			17.33
$J_{8,12}$	2.35	5.66	
		9.99	
$J_{11,12}$	7.41		

[a] *syn* relative to the cycloheptatriene double-bond system.
[b] The assignment of 12-H_{syn} and 12-H_{anti} is uncertain.

The NMR spectra of *(4)*, *(10)*, and *(11)* show, as expected, analogous splitting patterns. The vinylic protons of the cycloheptatriene structural unit appear as an AA'XX' system in each case, while the protons of the terminal double bonds give rise to one or more multiplets occurring at higher field. The signals at highest field belong to the proton 11-H_{syn}[**] located above the cycloheptatriene structural moiety of *(4)* and *(10)*.

On close comparison of the spectra by means of the data in Table 1 the near relationship of *(4)* and *(10)* to one another and to compound *(11)*, our model for a non-delocalized cycloheptatriene, can be clearly recognized. In particular it can be seen that these three compounds display remarkable similarity in the NMR parameters of the protons of the cycloheptatriene structural moiety and in those of the vinylic protons 7-H and 10-H. However, *(4)* differs distinctly from 1,6-methano[10]annulene, where the double bonds are integrated in the peripheral cyclically conjugated 10π-electron system, both as regards the chemical shifts of the vinylic protons 2-H to 5-H (as well as 7-H to 10-H) and as regards the alternation of the vicinal coupling constants $J_{2,3}$ and $J_{3,4}$[13].

The consequence of these findings is that *(4)* has the π-electron structure of a 1,6-divinylcycloheptatriene and that there is no compelling reason to describe the compound by homoaromatic structures such as *(5)* and *(6)*.

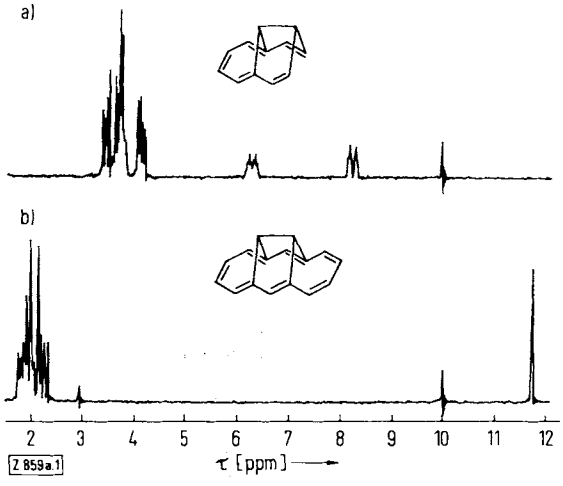


Fig. 1. ^{1}H-NMR spectra of a) tricyclo[5.4.1.$0^{4,12}$]dodeca-2,5,7,9,11(1)-pentaene *(4)* (in CCl_4) and b) 1,6:8,13-ethanediylidene[14]annulene *(7)* (in $CDCl_3$) (60 MHz; TMS as internal standard).

The assumption that the highly reactive *(4)* exists as the cyclically delocalized *(6)* appears wholly unrealistic if its NMR spectrum is compared with that of *(7)*. As is shown in Figure 1, the transition from *(4)* to *(7)* shifts the resonances of the corresponding vinylic protons by 1.2 to 1.9 ppm downfield and that of the bridge proton (11-H[**] and 15-H, respectively) by 3.6 ppm upfield. In view of such dramatic shifts it is beyond doubt that *(7)* owes its electronic and thermodynamic stability mainly to the peripheral delocalization of the 14π-electron system.

Comparison of UV spectra also fails to disclose any peculiarity in the π-electron structure of *(4)*. The UV spectra of *(4)*, *(10)*, and *(11)* are found to be very similar to one another and to correspond in type to those of 1,6-dialkylcycloheptatrienes[11]. By contrast, the spectrum of the delocalized 1,6-methano[10]annulene is related to that of benzene.

The parallelism recently reported between the ^{13}C-NMR spectra of *(4)* and 1,6-methano[10]annulene[14], which

[**] For numbering see Table 1.

was interpreted in terms of *(6)*, was falsified by an error in assignment of the ^{13}C resonance signals[15].

The homoaromaticity problem with regard to *(4)* is referred by this finding back to the still unsolved problem of the extent to which cycloheptatrienes possess homoaromatic character. The methods used here are clearly not sensitive enough to disclose homoconjugative interactions within *(4)*.

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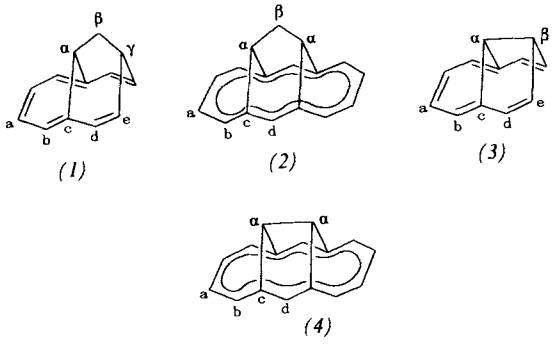
Significance of Stereochemical Factors for the Chemical Shift of the ^{13}C Resonance[**]

By *Harald Günther*, *Hans Schmickler*, *Udo H. Brinker*, *Klaus Nachtkamp*, *Jürgen Wassen*, and *Emanuel Vogel*[*]

Previous experience[1] has shown that the nuclear magnetic ^{13}C resonance frequency is sensitively influenced by stereochemical factors such as conformation, ring size, and ring strain but on the other hand is not significantly dependent on the π-electron structure of unsaturated cyclic systems. In particular, the ring current effect here plays only a minor role[2, 3]. Attempts to use ^{13}C-NMR data as criteria of aromaticity in comparative studies of olefinic and potentially aromatic systems[4–6] are not without risk, as we shall show for the cases of compounds *(1)*—*(4)*[7–9].



^1H-NMR spectra show unambiguously that *(1)* and *(3)* are olefinic[7], but that *(2)* and *(4)* are delocalized [14]annulenes[8, 9]. In contrast thereto, it follows from Table 1 that in ^{13}C-NMR spectroscopy the stereochemical relationship is dominant: according to the criterion of maximum agreement of the resonance frequencies, *(1)* must be ranked alongside *(2)*, and *(3)* alongside *(4)*, whereas the related electronic structures of the compound pairs *(1)*/*(3)* and *(2)*/*(4)* cannot be deduced from the ^{13}C data.

Table 1. δ(^{13}C) data for compounds *(1)*—*(4)* [a].

	C_c	C_a	C_b	C_d	C_e	C_α	C_β	C_γ
(1)	*119.5*	120.4	125.3	127.3	114.0	29.9 (33.8)	*24.1*	33.8 (29.9)
(2) [2]	*111.9*	*127.0*	*130.0*	*127.7*	—	*28.8*	*18.7*	—
(3)	*136.4*	*127.6*	131.3	133.5	115.1	*46.2*	*55.0*	—
(4)	*131.4*	*126.5*	*122.8*	*132.4*	—	*42.8*	—	—

[a] All values in ppm, referred to internal TMS; solvent $CCl_4/CDCl_3$ (5:1); conc. 0.1 M. Experimentally confirmed assignments are italicized, alternative possible assignments are given in parentheses. The spectra were measured on a Bruker-HX-90 instrument at 22.63 MHz with ^1H broad band decoupling by the Fourier transform technique.

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[**] Applications of ^{13}C Resonance Spectroscopy, Part 7. This work was supported by the Deutsche Forschungsgemeinschaft.—Part 6: *H. Günther*, *H. Schmickler*, *W. Bremser*, *F. A. Straube*, and *E. Vogel*, Angew. Chem. *85*, 585 (1973); Angew. Chem. internat. Edit. *12*, 570 (1973).

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[9] *E. Vogel* and *H. Reel*, J. Amer. Chem. Soc. *94*, 4388 (1972).

[10] Low-temperature measurements gave no indication that *(3)* might be engaged in valence tautomerism.

Only after the steric contribution to the ^{13}C-NMR shift has been largely eliminated by the comparisons *(1)/(2)* and *(3)/(4)* is it possible to recognize the high field shift for the bridging C atoms C_α and C_β of the annulenes which is partially due to the ring current effect. From this it is clear that no ring current is induced in *(3)*, and the compound is not to be regarded as homoaromatic.

This finding contradicts the interpretation of the ^{13}C-NMR spectrum of *(3)* by *Wenkert et al.*[6], who considered *(3)* to be the first neutral homoaromatic compound. Further, these authors assigned the resonance of C_c incorrectly and thus fortuitously established agreement with the resonance frequency of C-1,6 in 1,6-methano[10]annulene (114.6 ppm[2]). Figure 1 shows the relevant off-resonance experiment[1], whereby the signal at 136.4 ppm can be unambiguously recognized as the C_c resonance[10].

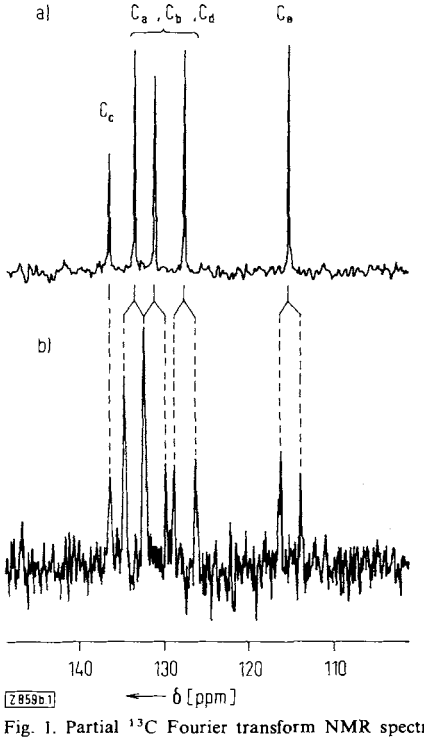

Fig. 1. Partial ^{13}C Fourier transform NMR spectrum of *(3)*: a) with ^1H broad band decoupling, b) off-resonance ^1H-decoupling.

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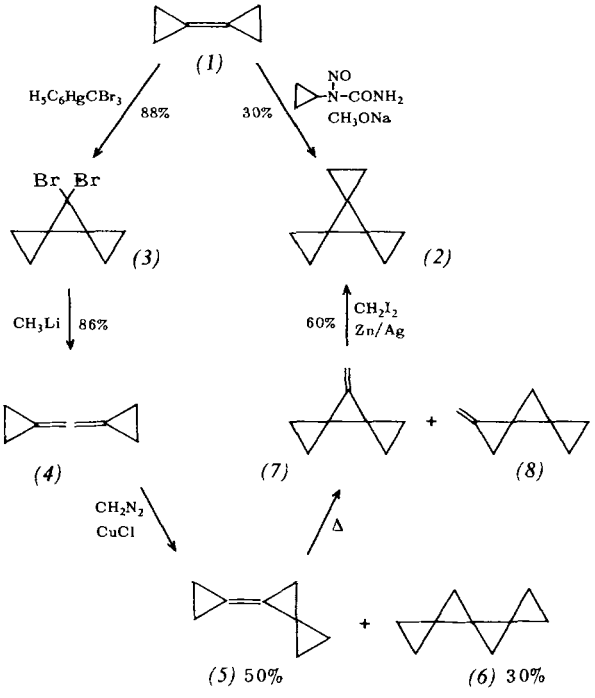
Thermal Isomerization of Cyclopropylidenespiropentane—An Unusual Route to Tricyclopropylidene ([3]-Rotane)[***]

By *Lutz Fitjer* and *Jean-Marie Conia*[*]

Starting from the observation that bicyclopropylidenes can be isomerized selectively to alkylidenespiropentanes under suitable conditions of thermolysis[2,3], we have developed a second synthesis for tricyclopropylidene ([3]-rotane) *(2)*[1], the key step being thermal isomerization of cyclopropylidenespiropentane *(5)*.

Treating bicyclopropylidene *(1)*[4] with (phenylmercuri)-tribromomethane as source of dibromocarbene[5] affords an 88% yield of 7,7-dibromodispiro[2.0.2.1]heptane *(3)* (m. p. 71 °C), which is converted by ethereal methyllithium solution into dicyclopropylidenemethane *(4)*[6] in 86% yield; the last product polymerizes with great ease.

Reaction of *(4)* with diazomethane under catalysis by CuCl[7] was then followed by gas chromatography and, if the cyclopropanation was broken off at the proper time, afforded up to 50% of cyclopropylidenespiropentane *(5)*. The trispiro[2.0.0.2.1.1]nonane *(6)* also formed could be obtained as main product by using an excess of diazomethane and is of interest as an "open chain" isomer of *(2)*. For example, we expect that experimental determination of the total strain energies of *(2)* and *(6)* will confirm the deduction, from ^1H-NMR, ^{13}C-NMR and UV spectroscopic data[1], that *(2)* does not contain a cyclic delocalized electron system.



Thermolyses of *(5)* were carried out at 210 °C and (to avoid dimerizations[8]) at 150—200 torr. The thermolysates were then investigated by gas chromatography.

After 1 h the thermolysate contained, along with 5% of unchanged *(5)*, a mixture of methylenedispiro[2.0.2.1]heptanes *(7)* and *(8)* (13:87) as sole products. After 12 h no *(5)* could be detected, but the product ratio *(7)/(8)* remained unchanged. Pure *(8)* proved to be stable under the above thermolytic conditions.

The final cyclopropanation of 7-methylenedispiro[2.0.2.1]-heptane *(7)* was achieved by use of a modified Simmons-Smith reaction[9] and led to a 60% yield of tricyclopropylidene ([3]-rotane) *(2)*, which was identified by comparison with authentic material[1].

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The IR, ^{1}H-NMR and UV spectroscopic data and high-resolution mass spectra of the new compounds *(3)*—*(8)* accord with the structures assigned above.

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

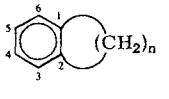
[8] If the thermolysis is carried out in the liquid phase under otherwise identical conditions, dimerization becomes the main reaction: *L. Fitjer* and *J. M. Conia*, to be published.

[9] *J. M. Denis, C. Girard*, and *J. M. Conia*, Synthesis *1972*, 549 (Zn/Ag couple, working up changed by acid hydrolysis). An attempt to obtain *(2)* by CuCl-catalyzed treatment of *(7)* with diazomethane [7] failed.

^{13}C-NMR Spectra of Benzocycloalkenes[**][***]

By *Harald Günther, Günther Jikeli, Hans Schmickler*, and *Jörn Prestien*[*]

Observations made for bridged annulenes[1, 2] indicate that the chemical shift of carbon-13 is influenced also by ring strain[3]. In order to study this aspect in greater detail, we have measured the ^{13}C-NMR spectra of the benzocycloalkenes *(1)*—*(6)* (Table 1)[4].



(1), n = 1 *(4)*, n = 4
(2), n = 2 *(5)*, n = 5
(3), n = 3 *(6)*, n = 6

Of the resonances of the aromatic carbon atoms only those of C-3,6 and C-4,5 show a systematic trend with extreme values in the case of *(4)* that conforms qualitatively with the ring strain changes in cycloalkanes and -alkenes[6]. For *(1)*—*(3)* $\delta(3,6) < \delta(4,5)$, whereas for *(4)*—*(6)* the reverse order holds. Results for ethyl-, *n*-propyl-, and *n*-butylbenzene[3a] allow the following δ-values to be calculated for the aromatic carbons in 1,2-dialkylbenzenes: δ(1,2) 143.2; δ(3,6) 128.3; δ(4,5) 125.5 ppm. These data agree well with those measured for 1,2-diethylbenzene *(7)* (Table 1) with the exception of an *ortho*-effect of 2.2 ppm. Similarly, the δ-values for *(5)* and *(6)* deviate only slightly from those predicted. Significant differences are observed, however, for *(4)* [δ(1,2)], *(2)* and *(3)* [δ(3,6)], as well as for all carbon atoms of *(1)*. With *(7)* as model the following "ring contributions" $\Delta\sigma_{ring}$ (Table 2) for the shielding of the aromatic carbons in *(1)*—*(6)* (in ppm) are obtained.

Table 2. $\Delta\sigma_{ring}$ [ppm] for the *o*-phenylene C atoms in *(1)*—*(6)*.

	C-1,2	C-3,6	C-4,5
(1)	+15.6	+13.3	−3.1
(2)	− 4.2	+ 5.9	−0.8
(3)	− 2.3	+ 4.0	−0.1
(4)	+ 4.6	− 0.8	+0.5
(5)	− 1.7	− 0.7	0
(6)	+ 0.4	− 0.7	+0.3

No linear correlation including all compounds exists between ring strain and the $\delta(^{13}C)$- or $\Delta\sigma_{ring}$-values. The $\Delta\sigma_{ring}$-values for C-3,6 and C-4,5 in *(1)*—*(3)* are, however, linearly dependent on the ring strain per CH_2-group in cyclopropene, cyclobutene, and cyclopentene[6]. For $\delta(^{13}C)$ and $^1J(^{13}C, ^1H)$ a general tend becomes apparent: in the case of C-3,6 and the α-CH_2 group increased shielding is accompanied by an increase in $^1J(^{13}C, ^1H)$. The same is true for the corresponding data[3a] in cycloalkanes up to cycloheptane. Present theory of carbon chemical shifts does not offer a simple explanation.

Table 1. ^{13}C chemical shifts [a] and one bond ^{13}C,H coupling constants [b] for benzocycloalkenes.

	δ(1,2)	δ(3,6)	δ(4,5)	δ(α-CH_2)	δ(β-CH_2)	δ(γ-CH_2)	^1J(3,H)	^1J(4,H)	^1J(α,H)
(1)	125.4	114.7	128.8	18.4	—	—	168.5	159	170
(2)	145.2	122.1	126.5	29.5	—	—	162	157.5	138
(3)	143.3	124.0	125.8	32.7	25.2	—	155.5	157	127
(4)	136.4	128.8	125.2	29.3	23.3	—	155	159	126
(5)	142.7	128.7	125.7	36.6	28.2	32.6	155	161	123
(6)	140.6	128.7	126.0	32.1	25.8 [c]	32.1 [c]	155	160	—
(7)	141.0	128.0	125.7	25.3	15.3	—	154	159	126

[a] In ppm downfield from internal TMS; conc. was 0.1—1 M in $CCl_4/CDCl_3$ (3:1); exp. error ±0.1 ppm.
[b] In Hz, maximum experimental error ±1.3 Hz; calculations for AA'BB'X spin systems showed that the error introduced by using first order treatment for the determination of the one bond coupling constants is less than 1 Hz.
[c] Assignment based on comparison with *(5)*.

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[**] Applications of ^{13}C-Resonance Spectroscopy, Part 8. This work was supported by the Deutsche Forschungsgemeinschaft.—Part 7: ref. [2].

[***] *Note added in proof* (August 23, 1973): *E. L. Motell, D. Lauer*, and *G. E. Maciel*, J. Phys. Chem. *77*, 1865 (1973), have just reported ^{13}C-data for *(1)*—*(7)*. The assignments given there for *(1)*—*(3)* are, however, incorrect and conclusions based thereon must be revised.

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[3] For other steric effects see: a) *J. B. Stothers:* Carbon-13 NMR Spectroscopy. Academic Press, New York 1972; b) *W. M. Beckenbaugh, S. R. Wilson,* and *P. A. Loeffler,* Tetrahedron Lett. *1972,* 4821.

[4] All spectra were recorded with simultaneous ^1H broad-band decoupling at 22.63 MHz using a Bruker HX-90 spectrometer. Assignments of ^{13}C resonance frequencies are based on "off resonance" broad-band decoupling, "off resonance" CW-decoupling, intensity measurements, observation of "fingerprints" [5], and specific deuteration.

[5] *H. Günther, H. Schmickler,* and *G. Jikeli,* J. Magn. Resonance, in press.

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CIDNP-Detection of a Photocatalyzed C—C Cleavage upon UV Irradiation of Glycolaldehyde in Aqueous Solution

By *Karl-Gerhard Seifert* and *Joachim Bargon*[*]

Glycolaldehyde *(1)* may be considered as the simplest of all sugars and as a model for the higher aldoses. Its unknown photochemical behavior is of interest in biochemistry.

We have studied the photolysis of *(1)* in aqueous solution with the Chemically Induced Dynamic Nuclear Polarization (CIDNP) method[1]. The NMR spectrum of *(1)* is rather complex because in water *(1)* is in equilibrium with two dimeric forms and with its hydrate. The monomeric aldehyde accounts for only 4% of the material in aqueous solution[2], and gives rise to the weak resonance lines at $\delta = 9.7$ (formyl proton) and $\delta = 4.5$ ppm (methylene protons)[3a].

Upon irradiation[3b] of a neutral solution of *(1)* in D_2O inside the modified probe of a Varian HA 60 NMR spectrometer these two lines turn into emission. Another emission line at $\delta = 3.5$ ppm is due to the photoproduct methanol *(2)* (Fig. 1).

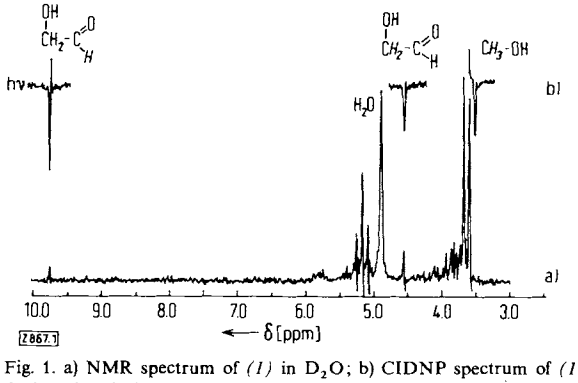

Fig. 1. a) NMR spectrum of *(1)* in D_2O; b) CIDNP spectrum of *(1)* during photolysis.

We explain these observations according to the qualitative rules of CIDNP[1,4]. Upon irradiation *(1)* cleaves from an excited triplet state into a radical pair of a formyl and a hydroxymethyl radical with triplet spin multiplicity[5].

$$\underset{(1)}{HOCH_2CHO} \xrightarrow{h\nu} \left(\overline{HOCH_2^{\bullet} \quad {}^{\bullet}CHO}\right)_T$$

This radical pair may then recombine to form *(1)* or disproportionate into CO and *(2)* in the solvent cage, which explains the negative polarization of *(1)* and *(2)*. Because of the large hyperfine coupling constant of the formyl radical ($a_H = +136$ G)[6] the aldehyde proton in *(1)* shows a much stronger polarization than the two methylene protons which experience a much smaller hyperfine coupling in the hydroxymethyl radical ($a_H = -17$ G)[7].

$$2\left(\overline{HOCH_2^{\bullet} \quad {}^{\bullet}CHO}\right) \longrightarrow \underset{(1)}{HOCH_2CHO} + \underset{(2)}{CH_3OH} + CO$$

An alternative pathway to *(2)* would be hydrogen abstraction by the hydroxymethyl radical. This possibility can be excluded, because in this case *(2)* should appear in enhanced absorption. In order to show that the starting material does not become polarized by an intermolecular photoreduction we have tried to identify the free-radical intermediates. We added some drops of CCl_4 to the D_2O solution of *(1)* and observed strongly polarized chloral hydrate (emission). The chloral is formed by random phase encounter of a formyl and a trichloromethyl radical proving the occurrence of free formyl radicals in aqueous solution during irradiation and thus the polarization of *(1)* by cleavage of the C—C bond (Norrish type I decomposition).

In presence of CCl_4 the CIDNP spectrum changes significantly: the starting material no longer shows a significant polarization in its aldehyde form, instead it exhibits emission in its *hydrated* form. Apparently, *(1)* is still photolyzed in its aldehyde form, but after recombination of the radical pair it becomes hydrated so fast that the polarization is transferred to its hydrate. We explain the accelerated rate of hydration in the presence of CCl_4 as an acid catalysis through HCl formation. This occurs after a formyl radical abstracts a chlorine atom from CCl_4, yielding formyl chloride, which decomposes into HCl and CO. This assumption is substantiated by the observation of CIDNP in the hydrate of *(1)* after adding traces of acid (HCl or HCOOH) to CCl_4-free solutions of *(1)* in D_2O. Formic acid is also a photoproduct in acid solution (Fig. 2).

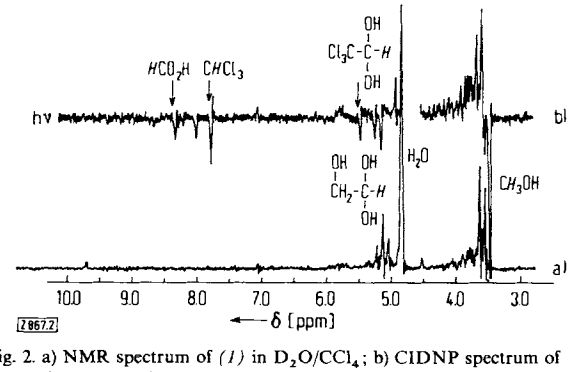

Fig. 2. a) NMR spectrum of *(1)* in D_2O/CCl_4; b) CIDNP spectrum of *(1)* during photolysis.

The CIDNP spectrum did not change after an addition of a little acetone to the D_2O solutions, indicating that even in the presence of acetone the primary photochemical step is the α cleavage of *(1)*.

The photolysis of formaldehyde in the presence of CCl_4 yields the same products as that of *(1)*. Hence, formaldehyde is photoreduced in its triplet state which results in

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the same radical pair as above with the same spin multiplicity (triplet)[8].

These experiments demonstrate possible applications of the CIDNP method in investigating reaction mechanism and the kinetics of photoreactions. In particular they allow the determination of hydration rates.

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[3a] Downfield from TMS as external standard.

[3b] The sample was irradiated with a 5 KW Hanovia 932 B39 high pressure mercury-xenon lamp, filtered through water in an all-quartz apparatus.

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[8] *J. Bargon* and *K. G. Seifert*, to be published.

Tricarbonyl-(1-phenylborinato)manganese[1]

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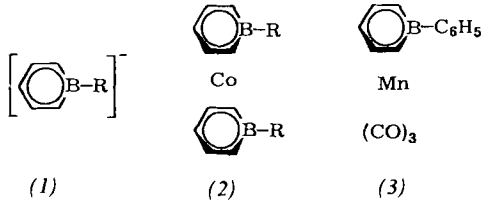
Dedicated to Professor Karl Winnacker on the occasion of his 70th birthday

Complexes containing the borabenzene (C_5H_5B, borine) system have been previously described only with cobalt as a central metal: Thus reaction of bis(cyclopentadienyl)-cobalt with boron-halogen compounds affords sandwich complexes of cobalt in which borinate ions *(1)*[2] are bound as hexahapto ligands to the central metal atom[3]. We have now tried to prepare borinato complexes of other metals by ligand transfer[4].



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

The paramagnetic bis(borinato)cobalt complexes *(2)*[3a, 3c], which contain an excess electron and thus labilized ring-metal bonds, should be excellent starting materials for ligand transfer reactions. Indeed, bis-(1-phenylborinato)co-balt *(2)*, $R=C_6H_5$, reacts with $Mn_2(CO)_{10}$ in boiling toluene with formation of metallic cobalt, thus yielding tricarbonyl-(1-phenylborinato)manganese *(3)*:

$$Co(C_5H_5B{-}C_6H_5)_2 + Mn_2(CO)_{10} \rightarrow$$
$$2\,Mn(CO)_3(C_5H_5B{-}C_6H_5) + Co + 4CO$$

The structure of the new complex[5] follows to a large extent from the mass spectrum. The dominant mode of decomposition is seen to be successive removal of the three CO groups ($m^* = 238.7$, –, 183.3) and of the Mn atom ($m^* = 112.5$)[6]; the fragment ion $[C_5H_5B{-}C_6H_5]^+$ then decomposes further in the known manner[3a] by loss of H_2 ($m^* = 149.0$) or of C_2H_2 molecules ($m^* = 105.4$, 80.3). A surprise is the appearance of the ion $[MnC_6H_5]^+$ which is probably formed from $[MnC_5H_5B{-}C_6H_5]^+$ by rearrangement and loss of C_5H_5B [borabenzene (?)].

The IR spectrum shows three νCO bands of high and similar intensity, which is the characteristic picture of a $M(CO)_3$ group with strong perturbation of the C_{3v} symmetry by the counterligand. The wave number for these bands is, in the mean, about 19 cm^{-1} higher than for those of $Mn(CO)_3(C_5H_5)$. This indicates that the $(C_5H_5B{-}R)$ ligand (here $R=C_6H_5$) is an appreciably stronger acceptor and weaker donor than the C_5H_5 ligand, a conclusion previously derived from the mass spectrometrically determined ionization energies of borinatocobalt complexes[3c].

That an intact 1-phenylborinate ligand *(1)* is present in *(3)* follows unambiguously also from a comparison of the ^1H- and ^{11}B-NMR spectra of *(3)* with those of the $[Co(C_5H_5)(C_5H_5B{-}C_6H_5)]^+$ ion *(4)*[3a]. The proton signals of the borabenzene portion appear at higher field for the molecule *(3)* in contrast to those of the cation *(4)* and, furthermore, can be completely analyzed and assigned by a first order procedure. Cyclic conjugation of the borabenzene ring and a negative charge on the boron have been proved for the free ligand *(1)*[2]. All the proton signals of the borabenzene ring in the complex

Table 1. Data for tricarbonyl-(1-phenylborinato)manganese *(3)*.

M. p. 85.5—86.5 °C.

MS (50 eV): *m/e* ($I_{rel.}$ [%]) 292(17; $Mn(CO)_3L^+$ with $L^- = (1)$), 264(3; $Mn(CO)_2L^+$), 236(20; $Mn(CO)L^+$), 208(100; MnL^+), 153(13; L^+), 151(7; $L^+ - H_2$), 132(4; $MnC_6H_5^+$, not $MnC_5H_5BH^+$), 127(7; $L^+ - C_2H_2$), 120(4, $MnC_5H_5^+$), 101(4; $L^+ - 2C_2H_2$), 55(40; Mn^+); $m^* = 238.7(292 \rightarrow 264)$, 183.3(236→208), 159.2(208→182), 149.0(153→151), 112.5(208→153), 105.4(153→127), 80.3(127→101).

IR (in *n*-hexane) [cm^{-1}] [a]:

(3)	2039	1974	1960
$Mn(CO)_3(C_5H_5)$	2028	1944	

Further bands of *(3)*: 1410, 1378, 1363, 1321, 1166, 1143, 1119, 1038, 983, 949, 917, 856, 812, 775, 766, 744, 739, 695, 661

^1H-NMR (τ values [ppm] and coupling constants [Hz]):

	(3) [b]	*(4)* [c] [3a, 3b]	*(1)* [d]
C_6H_5	2.0 m (2H)	2.0 m (2H)	1.9—2.0 m (2H)
	2.5 m (3H)	2.6 m (3H)	2.4—2.8 m (5H)
H^3, H^5	3.64 dd (2H)	3.1 m (3H)	
H^4	4.11 t (1H)		3.66 t (1H)
H^2, H^6	5.03 d (2H)	3.83 d (2H)	3.05 d (2H)
J_{23}	9.0	9.0	10.0
J_{34}	6.0	[e]	6.5

^{11}B-NMR (δ values [ppm]):

(3)	-24.6 ± 1.0 [f]
(4)	-23.3 ± 0.5 [f] [3a, 3b]
(1)	-27 [d, g]

[a] LiF optics were used for recording the νCO bands and NaCl optics for the other bands.
[b] In $[D_6]$-acetone (60 MHz, room temp.); measured relative to $[D_5]$-acetone (τ = 7.91 ppm).
[c] In $[D_6]$-acetone.
[d] In $[D_8]$-THF [2].
[e] Not determined.
[f] In $[D_6]$-acetone; measured relative to external $(C_2H_5)_2O{\cdot}BF_3$.
[g] Relative to $(C_2H_5)_2O{\cdot}BF_3$; δ = 59 ppm against external $B(CH_3)_3$ [2].

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(3) appear within a narrow range of 1.4 ppm and at relatively low field, as expected for complexes of cyclically conjugated ligands in general[7]; the ^{11}B signal is shifted slightly to higher field, as it is also for *(4)*. The borinate ligand in *(3)* thus retains its benzenoid character and, as in the known borinatocobalt complexes[3], is bonded to the Mn atom as an almost planar hexahapto ligand. An X-ray structure analysis confirms this conclusion[8].

Experimental:

A solution of $Co(C_5H_5B—C_6H_5)_2$ (300 mg, 0.83 mmol) and $Mn_2(CO)_{10}$ (650 mg, 1.66 mmol) in toluene (35 ml) is heated for 50 h under reflux (bath temp. 140 °C) and then filtered. The solvent is removed in a vacuum and the residue is chromatographed in pentane at −20 °C on a silica gel column (50 cm long, 1.2 cm wide). The highly mobile residue of $Mn_2(CO)_{10}$ is eluted, and then the main product is removed from the gel by CH_2Cl_2. After removal of the CH_2Cl_2, sublimation (high vacuum; 60—80 °C) affords analytically pure *(3)* (405 mg, 84%). The product crystallizes from organic solvents in pale yellow needles; it is stable in the solid state but in solution it is sensitive to light and to air.

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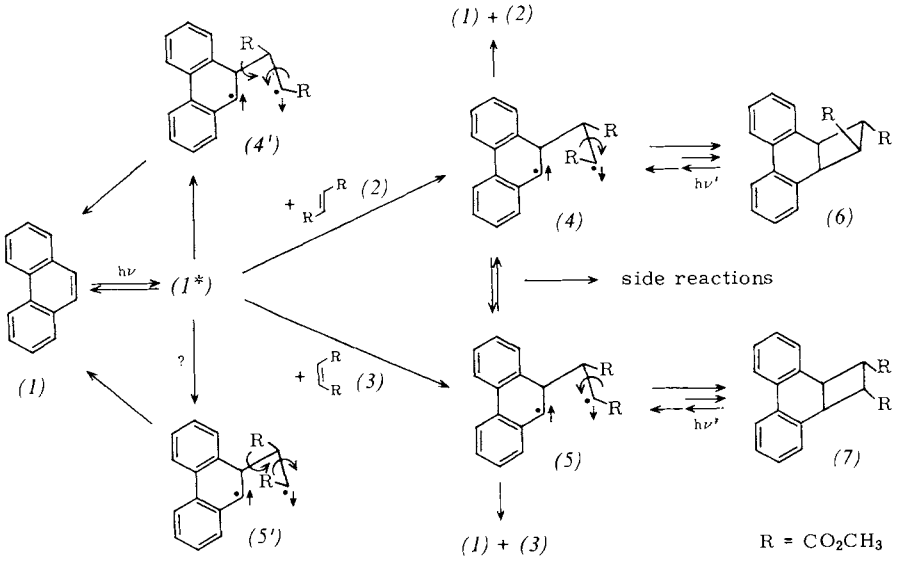
[2+2]-Photocycloadditions Involving Phenanthrene: Mechanistic Models for Two-Step Processes[**]

By *Gerd Kaupp*[*]

The continuing interest in concerted singlet and triplet photocycloadditions[1], and the experimental proof of kinetically operative intermediates among intramolecular models[2], lead to mechanistic decisions also for intermolecular examples. We now report our experimental results for a typical model system (fluorescence, selective excitation, no complicating *cis/trans* isomerization) for non-stereospecific $[2\pi+2\pi]$-photoadditions. Absence of stereospecificity indicates intermediates with internal rotation, but additional data are required to confirm the postulate of competing supra- and antara-facial additions[1]. This purpose can be achieved with photoadditions of phenanthrene *(1)*[3] to dimethyl maleate *(3)* and fumarate *(2)*, yielding *(6)* and *(7)*[4]. Meanwhile the result of these reactions has been interpreted by assumption of exciplexes[5,6] (electronically excited π-complexes with the possibility of luminescence) as well as by non-concerted triplet mechanisms[6]. However, a combination of measurements of product yield, quantum yield, and luminescence with the aid of molecular models leads to interpretation of



the near-constancy of the *(6)*:*(7)* ratio (see Table 1) on the basis of a two-step singlet mechanism[4].

The following findings are relevant to the proposed singlet mechanism:

1. The lifetime of the phenanthrene fluorescence ($\phi_{Fl}=0.13$) is relatively large at 57.5 ns[7].
2. The phenanthrene fluorescence is quenched to the extent of 92 and 48%, respectively, by *(2)* and *(3)* (4.5×10^{-2} mol/l; benzene).
3. The reaction with *(3)* is accelerated by oxygen, not decelerated.
4. The isomerization of the olefins *(2)* and *(3)*, sensitized by phenanthrene, is relatively slow in benzene and proceeds in both directions (see Table 1).

[1] Derivatives of Borabenzene, Part 2. This work was supported by the Deutsche Forschungsgemeinschaft and by Farbwerke Hoechst AG.—Part 1: [3a].

[2] The only free ligand known is lithium 1-phenylborinate: *A. J. Ashe III*, and *P. Shu*, J. Amer. Chem. Soc. *93*, 1804 (1971).

[3] a) *G. E. Herberich* and *G. Greiss*, Chem. Ber. *105*, 3413 (1972); b) *G. Herberich*, *G. Greiss*, and *H. F. Heil*, Angew. Chem. *82*, 838 (1970); Angew. Chem. internat. Edit. *9*, 805 (1970); c) *G. E. Herberich*, *G. Greiss*, *H. F. Heil*, and *J. Müller*, Chem. Commun. *1971*, 1328; d) for X-ray data see *G. Huttner*, *B. Krieg*, and *W. Gartzke*, Chem. Ber. *105*, 3424 (1972).

[4] Other ligand transfers can be carried out with carbonyliron complexes; cf. *G. E. Herberich*, Chimia *26*, 475 (1972).

[5] Correct C, H, and Mn analyses have been obtained.

[6] General regularities in the decomposition of organometallic complexes in the mass spectrometer have been treated by *J. Müller*, Angew. Chem. *84*, 725 (1972); Angew. Chem. internat. Edit. *11*, 653 (1972).

[7] For a detailed discussion see [3a]; $\tau=5.04$ for $Mn(CO)_3(C_5H_5)$ and 4.40 for $Cr(CO)_3(C_6H_6)$ (both in $[D_6]$-acetone).

[8] *G. Huttner* and *W. Gartzke*, unpublished work.

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5. In ethyl bromide, which favors formation of triplet phenanthrene (fluorescence of phenanthrene is 12 times weaker in ethyl bromide than in benzene), a rapid conversion *(3)*→*(2)* occurs as well as formation of *(6)* and *(7)* (see Table 1).

Table 1. Selective irradiation of 1.12 mmol of phenanthrene *(1)* in the presence of 11.2 mmol of *(2)* or *(3)* [a].

Olefin	Solvent [ml]	Conversion [%]	Yield of *(6)* [%]	Yield of *(7)* [%]	*(2)*/*(3)* [b]
(2)	Benzene, 250	34	17.5	11.5	93/7
(3)	Benzene, 250	31	18	12	5.5/94.5
(2)	Benzene, 50	55	20	13.5	87/13
(3)	Benzene, 50	50	29	19	8/92
(3)	Benzene, 50 [c]	89	44	29	5/95
(3)	C_2H_5Br, 50	81	33	22	>99/1

[a] Immersed high-pressure mercury lamp Hanau Q-81; Wertheimer UVW-55 filter glass [% transmission: <1 (λ=315 nm); 12.5 (334); 31 (365); <1 (410)]; N_2; 20 °C; 12 h; any anthracene present as impurity in the phenanthrene was removed by irradiation of concentrated solutions, filtration and sublimation.
[b] After cessation of reaction.
[c] By passage of oxygen.

Not only the quenching data and the preparatively important influence of oxygen, but also the extent and direction of the sensitized *cis/trans* isomerizations, show that, under the experimental conditions, there is almost complete absence of spin reversal in the electronically excited phenanthrene unless this is accelerated by external heavy-atom effects. The fact that the *(6)*:*(7)* ratio is almost the same in all cases[8] proves interconversion of the intermediates *(4)* and *(5)*, a result that is indicated also by inspection of molecular models and an apparent discrepancy: the initial quantum yields for consumption of phenanthrene in reactions with *(2)* and *(3)* are almost the same within experimental error [ϕ=0.010; 4.5×10^{-2} mol/l of *(2)* or *(3)*; benzene; N_2], although *(2)* quenches the phenanthrene fluorescence much more effectively than does *(3)* (see above). Comparison of the sensitized olefin isomerizations under standard conditions (see Table 1) shows, however, that *(2)* isomerizes faster than *(3)*.

Clearly, with little variation in the geometry of its approach to electronically excited phenanthrene, the fumaric ester *(2)* yields two isomeric intermediate products *(4)* and *(4')*, whereby the ability to fluoresce is lost[9]. The *syn*-intermediate *(4')*, which at best can afford *(6)* but cannot afford *(7)*, then decomposes to phenanthrene and *(2)* or *(3)*, because, again in agreement with molecular models, the steric hindrance and simultaneously the orbital overlap of the radical centers are decreased by partial rotation around the newly formed σ-bond. The reaction with *(3)* does not require the rather improbable assumption of *(5')*. In the *anti*-rotamers *(4)* and *(5)* the orbital overlap is more favorable for formation of a four-membered ring, leading to *(6)* or *(7)* (cf. also Ref. [2]), but the decomposition to *(1)* and *(2)* or to *(1)* and *(3)* preponderates as shown by the low quantum yields.

Table 2. 313 nm irradiation of 10^{-3} mol/l of *(6)* and *(7)* [a]; yields of phenanthrene *(1)* [b] and quantum yields (ϕ) [c].

Medium	Yield of *(1)* [%] from *(6)*	ϕ	Yield of *(1)* [%] from *(7)*	ϕ
CH_3CN/N_2	95	0.75	82	0.45
CH_3CN/O_2	96	0.8	80	0.4
1.0 mol/l *trans*-piperylene in CH_3CN/N_2	92	0.75	67	
C_2H_5Br/N_2	50	0.45	35	

[a] Band pass 4.8 nm; 20 °C.
[b] UV analysis after complete conversion.
[c] Formation of phenanthrene after up to *ca.* 30% conversion.

Further confirmation of the formula scheme is provided by irradiation of *(6)* (m.p. 114 °C)[10] and *(7)*[11] (m.p. 116 °C). Phenanthrene is formed from *(6)* (excitation of the longest wavelength band) faster than from *(7)* (see Table 2); and *(7)* can be isolated by chromatography after partial or extensive reaction of *(6)*, in agreement with the mechanism for the intermediates.

Further indications are given by the differing intensities of fluorescence [*(6)*: ϕ_{Fl}=0.015; *(7)*: ϕ_{Fl}=0.15; cyclohexane/N_2; 20 °C; $\lambda_{Fl.}^{corr.}$=311, 326, 337 sh, 355 sh, 375 sh; Stokes shift: 4 nm] and rates of photolysis [*(6)* faster than *(7)*] at −190 °C (ether/alcohol glass[12]). Since these findings show absence of appreciable thermal activation barriers in the photoreversions, in spite of the competing luminescence, it again becomes clear that stepwise mechanisms apply that involve the least possible geometrical and chemical change, and it must be concluded that the *cis*-disubstituted bond of the four-membered ring of *(6)* is cleaved first [cf. *(7)*].

Further, the photoreversions occur without temporary change in multiplicity, as shown by determinations of quantum yield and product yield under various conditions (see Table 2):

1. Oxygen has no appreciable effect on the quantum yield or yield of phenanthrene.

2. The usual triplet quencher, *trans*-piperylene, causes hardly any diminution in the rate of formation of phenanthrene from *(6)*; a decrease in the rate of formation of phenanthrene from *(7)* is to be expected owing to the lower yield of product.

3. In ethyl bromide there is no favorable heavy-atom effect on the formation of phenanthrene: lower initial rate and lower yield occur in parallel.

It is assumed that the rotamers *(4)* and *(5)* [also *(4')*] are partially trapped by materials added or formed during the reaction, yielding inhomogeneous (probably polymerizing) by-products, because phenanthrene is stable under the conditions of irradiation even for a prolonged time. The results show that very different observations, which could not be precalculated by the method of potential energy hypersurfaces[13], can however be brought together in a single scheme on an empirical-experimental basis[14]. Experiment indicates that variations in initial quantum yield under the influence of triplet quenchers or of possible heavy-atom effects should be interpreted on the basis of triplet mechanisms only if the product yields do not vary simultaneously.

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[1] *R. B. Woodward* and *R. Hoffmann*: Conservation of Orbital Symmetry, 2. Edit., Verlag Chemie, Weinheim 1972; *N. D. Epiotis*, J. Amer. Chem. Soc. *94*, 1941 (1972).

[2] *G. Kaupp*, Angew. Chem. *83*, 361 (1971); Angew. Chem. internat. Edit. *10*, 340 (1971); Chimia *25*, 230 (1971); Angew. Chem. *84*, 259 (1972); Angew. Chem. internat. Edit. *11*, 313 (1972); Liebigs Ann. Chem. *1973*, 844.

[3] For further examples see *T. Miyamoto*, *T. Mori*, and *Y. Odaira*, Chem. Commun. *1970*, 1598.

[4] Lecture at a combined meeting of VÖCh and GDCh (May 1972) in Vienna [*G. Kaupp*, Allg. Prakt. Chem. *23*, 80 (1972)] and in the 4th IUPAC Symposium on Photochemistry (July 1972) in Baden-Baden [manuscripts of contributed papers: No. 32, p. 110 (1972)].

[5] *S. Farid, J. C. Doty*, and *J. L. R. Williams*, J. C. S. Chem. Commun. *1972*, 711; we also obtained acid-labile 1:1 adducts on incompletely selective irradiation with 350nm fluorescence lamps (Rayonet or Gräntzel reactor); however, the use of Wertheimer UVW-55 filter glass excludes excitation of *(2)* and *(3)*.

[6] *R. A. Caldwell*, J. Amer. Chem. Soc. *95*, 1690 (1973).

[7] *I. B. Berlman*: Handbook of Fluorescence Spectra of Aromatic Molecules. Academic Press, New York 1971.

[8] *(6)* and *(7)* are obtained in the ratio 3:2 also in acetonitrile—4.5% conversion *(3)* → *(2)*.

[9] No long-wave exciplex luminescence was observable alongside the residual monomer fluorescence when highly purified phenanthrene and *(2)* or *(3)* were used.

[10] NMR ($CDCl_3$), *(6)*: τ = 1.95—2.4 (2H, m); 2.55—3.1 (6H, m); 5.55—6.45 (4H, m); 6.25 (3H, s); 6.50 (3H, s); *(7)*: τ = 1.95—2.25 (2H, m); 2.5—2.8 (6H, m); 5.7—5.9 (2H, AA'BB'); 6.23 (6H, s); 6.45—6.65 ppm (2H, BB'AA'); the UV spectra of *(6)* and *(7)*, containing much fine structure, are almost superposable; both adducts are stable up to at least 230 °C for 24h.

[11] *D. Bryce-Smith* and *B. Vickery*, Chem. Ind. (London) *1961*, 429.

[12] Under these conditions a yellowish-green post-luminescence competes.

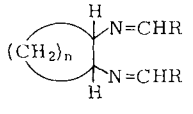
[13] I am very grateful to Professor *L. Salem* and Professor *N. D. Epiotis* for this information.

[14] Further examples and applications will be reported later.

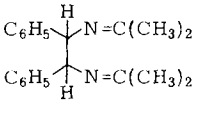
[3.3]-Sigmatropic Reactions in the *N,N'*-Dimethyleneethylenediamine System [**]

By *Fritz Vögtle* and *Ernst Goldschmitt* [*]

In 1965 *Staab* and *Vögtle*[1] described the first thermal valence isomerizations of two-fold Schiff bases of type *(1)*.



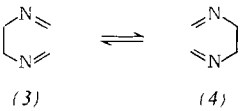
(1), n = 1,2



(2)

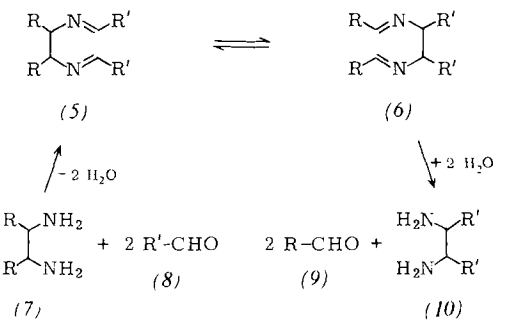
The original object of that work has not previously been achieved, namely to carry out, with compounds such as *(1)*, $n=4$, and *(2)*, [3.3]-sigmatropic rearrangements of type *(3)* ⇌ *(4)* that were not assisted by ring strain effects, in analogy to the Cope rearrangement[2,3].

It was therefore all the more surprising when, in connection with our studies of the hydrobenzamide-amarin valence



(3) *(4)*

isomerization[4], we found the valence isomerization that we had looked for was quite general for the system *(5)* ⇌ *(6)* when aromatic groups were present as substituents and that there it occurred under most unexpectedly mild conditions[5]:



(a), R = phenyl, R' = 2-pyridyl
(b), R = 2-hydroxyphenyl, R' = phenyl
(c), R = 2-hydroxyphenyl, R' = 4-methoxyphenyl
(d), R = 2-hydroxyphenyl, R' = 2-pyridyl

The rearrangement *(5a)* → *(6a)* (Table 1), which was the first that we observed, occurs so rapidly that the preparation and isolation of the Schiff base *(5a)* from *(7a)* and *(8a)* must be carried out cautiously at room temperature; even under "normal" conditions for synthesis of *(5a)*, *i.e.* in boiling benzene, a mixture of *(5a)* and *(6a)* is obtained. Further, if pure *(5a)* is heated at temperatures slightly above its melting point (181—182 °C), the separation of higher-melting crystals of the valence isomer *(6a)* can be seen (Table 1).

Table 1. Reactants, products, and hydrolysis products of the valence isomerizations *(5)* → *(6)* [a].

Cpd.	R	R'	Yield [%]	M.p. [°C]	^{1}H-NMR ($CDCl_3$, TMS = 0) δ [ppm] Ar—CH— (2H, s)	—N=CH—Ar (2H, s)	—NH_2 (4H, s)
(5a)	Phenyl	2-Pyridyl	68	181—182	4.91	8.14	—
(6a)	Phenyl	2-Pyridyl	76	190—192	5.28	8.27	—
(6b)	2-Hydroxyphenyl	Phenyl	96	207—209	4.77	8.06	—
(6c)	2-Hydroxyphenyl	4-Methoxyphenyl [b]	84	203—205	4.67	8.07	—
(6d)	2-Hydroxyphenyl	2-Pyridyl	91	247 (dec.)	—	—	— [c]
(10b)	—	Phenyl	93	119—120	3.94	—	1.23
(10c)	—	4-Methoxyphenyl	96	150—152	3.90	—	1.27
(10d)	—	2-Pyridyl [d]	68	73—75	4.29	—	1.79

[a] Satisfactory analytical values and mass spectra were obtained for all the substances recorded.
[b] Mol. wt. 470 (osmometric in $CHCl_3$); calc.: 480.6.
[c] The substance is sparingly soluble.
[d] Mol. wt. 221 (osmometric in $CHCl_3$); calc.: 214.3.

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In the 2-hydroxyphenyl-substituted systems *(5b)*—*(5d)* the threshold of valence isomerization lies still lower: the usual method for synthesis of these Schiff bases, namely treatment of α,α'-diamino-2,2'-bibenzyldiol *(7b)* with the aldehydes *(8b)*—*(8d)* in boiling benzene, affords only the rearrangement products *(6b)*—*(6d)*, the yields thereof being 84—96% (Table 1). Acid-catalyzed hydrolysis of the crystalline products *(6b)*—*(6d)* gave in all cases pure salicylaldehyde together with the 1,2-diarylethylenediamines *(10)* that are produced by C—C bond formation and are the "parents" of the valence isomers *(6)*; of these diamines, *(10b)* could be compared with the authentic substance prepared from amarin[6]. The new, water-soluble diamine *(10d)*, which cannot be obtained by the usual methods, can be obtained on a preparative scale (yield 68%) in this way, *i. e.* by the reaction *(5d)* → *(6d)*, followed by hydrolysis (Table 1).

As the examples *(b)* to *(d)* show, the equilibrium in the reaction *(5)* ⇌ *(6)* of the 2-hydroxyphenyl-substituted compounds lies completely on the side of the valence isomers *(6)*. That the conditions necessary are unusually mild in comparison with those for [3.3]-sigmatropic migration in corresponding biallyl systems (the Cope rearrangement)[7] is shown by fact that the rearrangement products

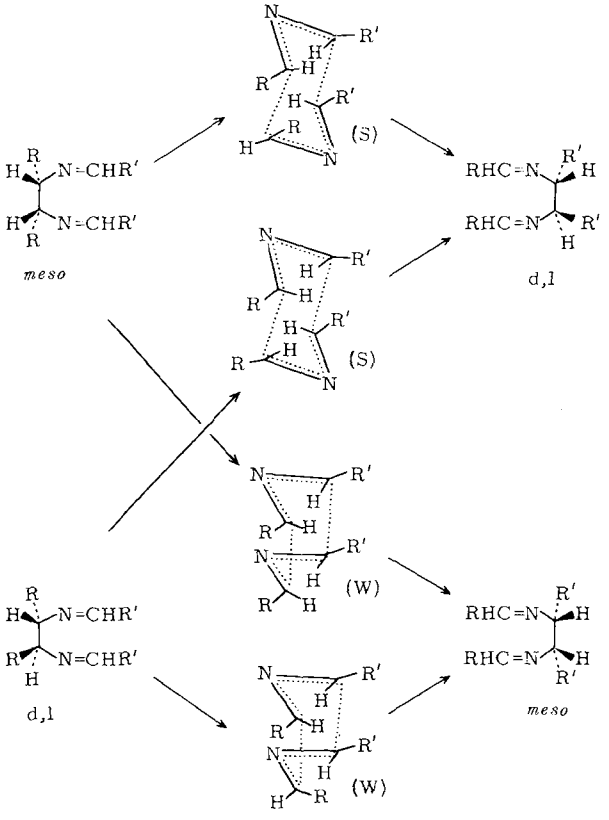

Fig. 1. Possible transition states for the valence isomerization *(5)* → *(6)* and their stereochemical consequences. S = chair-shaped and W = boat-shaped transition state.

(6b) and *(6d)* are isolated when preparation of *(5b)* and *(5d)* from, respectively, *(7b)* and benzaldehyde *(8b)* or from *(7b)* and 2-pyridinecarbaldehyde *(8d)* is attempted at room temperature; a possible explanation is that steric interactions during formation of the new C—C bond are smaller with compounds such as *(5)* than with compounds such as *(2)*, and, further, that hydrogen bonds[8] are formed that stabilize the hydroxyphenyl products *(6)*.

The isomerization observed is, however, by no means confined to cases where the substituent R is phenyl or 2-hydroxyphenyl: orienting experiments have shown that equilibrium mixtures of *(5)* and *(6)* arising by the valence isomerization are obtained also when the groups R and/or R' are varied within wide limits.

The Cope rearrangement is today formulated as a [3.3]-sigmatropic reaction of the type $[_{\sigma}2_s + _{\pi}2_s + _{\pi}2_s]$; for rearrangement of the carbon skeleton, the four-center transition state (chair form), required for reasons of orbital symmetry, has been proved by several examples[7]. However, sigmatropic [3.3]-shifts are by no means impossible in systems where the geometric relations enforce a boat-shaped transition state[9].

The starting point for our study of the stereochemical consequences in the "diaza-Cope" system is the expectation (Fig. 1) that a boat-shaped transition state will always lead to a *meso*-product *(6)*, independently of the stereochemistry of the reactant ethylenediamine *(7)*, provided that the C=N double bond has the *E* configuration[10] and that the [3.3]-shift is of the synchronous suprafacial type. We have found that the *meso*-diamines *(10b)* and *(10c)*[6] are obtained by valence isomerization of *(5b)* and *(5c)* and subsequent hydrolysis, but further studies with a large number of variously substituted compounds *(5)* and *(6)* are needed to decide whether it is justifiable to conclude therefrom that the boat form of the transition state is favored in our systems.

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[1] *H. A. Staab* and *F. Vögtle*, Tetrahedron Lett. *1965*, 51; Chem. Ber. *98*, 2701 (1965).

[2] *H. A. Staab* and *F. Vögtle*, Chem. Ber. *98*, 2691 (1965).

[3] *H. A. Staab, B. Berrang*, and *M. Schmidt*, personal communication.

[4] *D. H. Hunter* and *S. K. Sim*, J. Amer. Chem. Soc. *91*, 6202 (1969).

[5] For clarity and so as not to assume the stereochemistry of the reaction, C—H bonds are omitted from formulas *(5)*, *(6)*, *(7)* and *(10)*.

[6] *O. Fischer* and *G. Prause*, J. Prakt. Chem. *77*, 125 (1908); *M. Gullotti, A. Pasini, P. Fantucci, R. Ugo*, and *R. D. Gillard*, Gazz. Chim. Ital. *102*, 855 (1972).

[7] Review: *G. Maier*: Valenzisomerisierungen. Verlag Chemie, Weinheim 1972.

[8] *J. Bregman, L. Leiserowitz*, and *K. Osaki*, J. Chem. Soc. *1964*, 2086; *J. Bregman, L. Leiserowitz*, and *G. M. J. Schmidt, ibid. 1964*, 2068.

[9] *R. B. Woodward* and *R. Hoffmann*: The Conservation of Orbital Symmetry. Verlag Chemie, Weinheim 1970, p. 150 and note [206]; *W. von E. Doering* and *W. R. Roth*, Angew. Chem. *75*, 27 (1963); Angew. Chem. internat. Edit. *2*, 115 (1963).

[10] *J. Bernstein* and *G. M. J. Schmidt*, J. C. S. Perkin II, *1972*, 951.

Reaction of Imidic Esters with Aziridines[1]

By *Dieter Bormann*[*]

Dedicated to Professor Karl Winnacker on the occasion of his 70th birthday

In the presence of small amounts of ammonium bromide, cyclic imidic esters such as 2-methoxy-1-pyrroline *(1a)*

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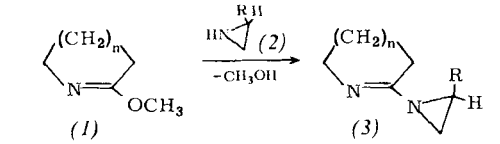
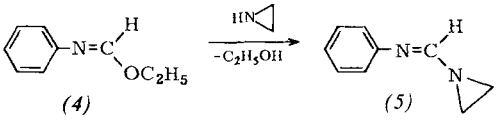
and 3,4,5,6-tetrahydro-7-methoxy-2*H*-azepine *(1b)* undergo a mild exothermic reaction with aziridines *(2)*, yielding 1-iminomethyl-substituted aziridines *(3)* (Table 1).



(1) *(3)*



(4) *(5)*

(a), n = 1; *(b)*, n = 3

The reaction takes place also with aziridine itself *(2)*, R = H, and with 2-methylaziridine *(2)*, R = CH_3, but fails under these conditions with 2,2-dimethylaziridine.

In the presence of ammonium bromide, ethyl *N*-phenylformimidate *(4)* undergoes a strongly exothermic reaction with aziridine *(2)*, R = H, even at *ca.* −10 °C, yielding compound *(5)* (Table 1).

being kept for 1 h at room temperature the solution is heated for 3 h under reflux; then the compounds *(6)* are distilled off.

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[1] Imino Esters and Their Reactions, Part 4.—Part 3: *D. Bormann*, Chem. Ber., in press.

[2] *H. Oediger, F. Möller*, and *K. Eiter*, Synthesis *1972*, 591.

The Nature of Carbocations Derived from Tricyclo[3.1.1.$0^{2,4}$]hept-6-yl and Tricyclo[3.2.0.$0^{2,7}$]hept-4-yl Systems[**]

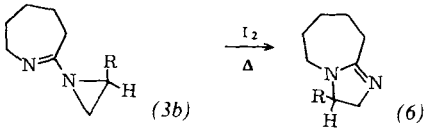
By *S. Masamune, M. Sakai, A. V. Kemp-Jones, H. Ona, A. Venot*, and *T. Nakashima*[*]

Successful generation of the structurally unique carbocation *(1)* of C_{4v} symmetry from the homotetrahedrane system *(2)*[1] has suggested that the solvolysis of *exo-anti*-tricyclo[3.1.1.$0^{2,4}$]hept-6-yl *p*-nitrobenzoate *(3a)*[2] may involve an ionic species *(4a)* of C_{2v} symmetry, a bis-homolog of *(1)*, or its equivalent. This anticipation has now been realized and we wish to demonstrate remarkable features of the carbocation.

Table 1. Compounds prepared.

Cpd.	Name	B. p. [°C/torr]	νC=N (CH_2Cl_2) [cm^{-1}]	n_D^{20}	Yield [%]
(3a), R = H	2-Aziridinyl-1-pyrroline	74/20	1634	1.4903	81
(3b), R = H	7-Aziridinyl-3,4,5,6-tetrahydro-2*H*-azepine	98/20	1658	1.4983	74
(3b), R = CH_3	3,4,5,6-Tetrahydro-7-(2-methyl-aziridinyl)-2*H*-azepine	92/20	1658	1.4900	71
(5)	*N*-(1-Aziridinylmethylene)aniline	105/5	1639	1.5795	28
(6), R = H	1,8-Diazabicyclo[5.3.0]dec-7-ene	108/10	1603	1.5122	90
(6), R = CH_3	10-Methyl-1,8-diazabicyclo-[5.3.0]dec-7-ene	105/10	1603	1.5008	89

The strongly basic aziridine derivatives *(3)* and *(5)* can be purified by distillation and, except for *(5)*, are stable for a long time; they give correct analytical figures. When heated with iodine, *(3b)*, R = H and CH_3, rearrange to 1,8-diazabicyclo[5.3.0]dec-7-enes *(6)* (Table 1). These strongly basic compounds can be used for dehydrohalogenations (for a review of the use of similar compounds see ref. [2]). Compounds *(6)*, R = H and CH_3, can be purified by distillation and give correct elemental analyses.



(3b) *(6)*

1-Iminomethyl-substituted aziridines (3):

NH_4Br (100 mg) is added to a mixture of the imidic ester *(1)* (1 mol) and aziridine (1.5 mol) at room temperature. After 8 hours' stirring without cooling, the compounds *(3)* are distilled off.

1,8-Diazabicyclo[5.3.0]dec-7-enes (6):

A solution of *(3b)*, R = H or CH_3 (0.3 mol), in acetone (100 ml) is treated with iodine (1.0 g). The solution becomes dark brown but the color fades after a few minutes. After

The 2,4-dideuterio derivative *(3b)* was prepared in a manner similar to that previously described[2, 3], but modified to provide a much improved overall yield. Thus, treatment of the dimethyl ester *(10a)* with sodium methoxide in CH_3OD and hydrolysis with D_2O (NaOD) effected incorporation of 1.8 deuterium atoms per molecule to provide *(10b)* which was converted without loss of deuterium into a dideuteriobicyclo[2.2.0]hexene derivative *(11a)* through acetylation and Kolbe electrolysis[4]. Solvolysis of the trifluoromethanesulfonate *(11b)* in acetic acid proceeded smoothly at room temperature ($\tau_{1/2}$ = approximately 45 min) to provide near-quantitative yields of bicyclo[2.1.1]hexen-5-yl acetate (1.8 D) *(12)*, which survived under the solvolytic conditions, so that the previous problem[3] arising from the facile 1,3-sigmatropic rearrangement of *(12)* is now solved. Conversion of *(12)* into *(3b)* (1.8 D) follows the earlier procedure.

The *p*-nitrobenzoate *(3b)* underwent solvolysis in 60% aqueous dioxane to afford *endo*-tricyclo[3.2.0.$0^{2,7}$]heptan-4-ol *(5a)* (*ca.* 70% yield) and the corresponding *p*-nitrobenzoate *(5b)* (*ca.* 20%). ^{1}H-NMR analysis shows that

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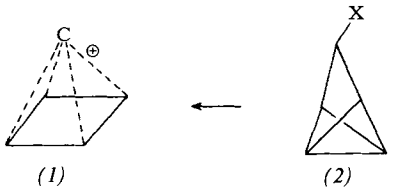
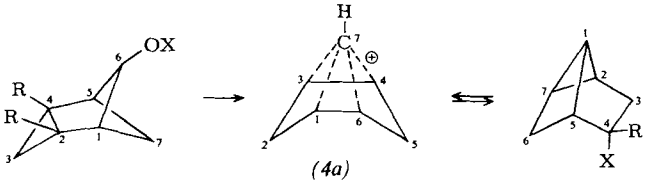
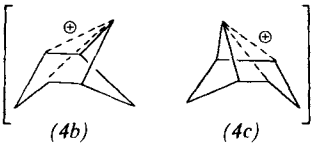


(1) (2)



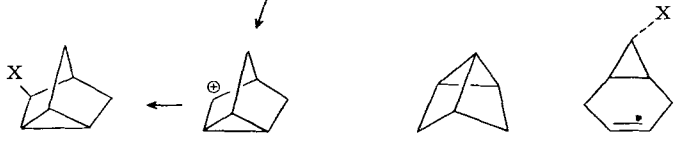
(4a)

(3a), R = H, X = NO_2–C_6H_4CO
(3b), R = D, X = NO_2–C_6H_4CO
(3c), R = H, X = COCl
(3d), R = D, X = COCl



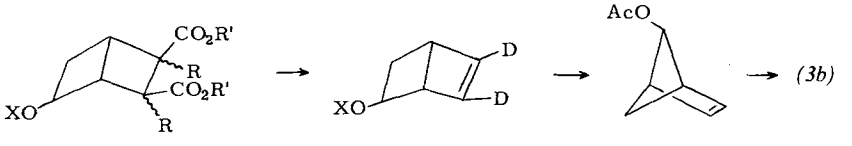
(4b) (4c)

(5a), R = H, X = OH
(5b), R = H, X = NO_2–C_6H_4COO
(5c), R = D, X = TsO
(5d), R = H, X = Cl
(5e), R = D, X = Cl
(5f), R = H, X = OCH_3



(6a), X = OCH_3
(6b), X = OH

(7) (8) (9)



(10a), R = H, R' = CH_3, X = Ac
(10b), R = D, R' = H, X = H

(11a), X = Ac
(11b), X = CF_3SO_2

(12) (3b)

C-4 of both products possesses 0.45 D rather than 0.9 D[5], and further the ^{13}C-NMR spectrum of *(5a)* was in accord with complete deuterium scrambling among C-2, C-4, C-5, and C-7 [δ_{TMS} ($CDCl_3$): 24.2, 78.4, 42.4, 19.4][6]. These results lead to the conclusion that the solvolysis of *(3a)* involves the intermediate cation *(4a)*, or that the equilibration of cations *(4b)* and *(4c)* of lower symmetry (C_s) is completed prior to solvent capture. Furthermore, the same cation (cations) is very likely to be responsible for the deuterium distribution observed in the acetolysis of the tosylate *(5c)*[7].

To gain further insight into the nature of the cations expressed by formulas *(4a)* or *(4b)* and *(4c)*, we have generated the long-lived ionic species from *(3c)*, *(3d)*, *(5d)* and *(5e)*[8], using superacid media. Solutions of *(3c)* and *(5d)* in a 1:5 mixture of SbF_5 and SO_2ClF at -110 °C provided identical ^{13}C-NMR and ^{1}H-NMR spectra[9]. The signal intensity and off-resonance spectra readily permitted assignment of the ^{13}C-NMR signals [δ_{TMS} = 39.38 (C-1), 8.09 (C-2), -17.15 ppm (C-7)][10]. The corresponding ^{1}H-NMR spectrum, which is consistent with the ^{13}C-NMR spectrum, showed three rather broad (partly due to the viscosity of the solution) signals at τ 5.89, 7.46, and 8.37 with the relative intensity 4:2:3 and the signal due to the proton at apical carbon-7[10] overlaps with those at C-2 (and C-5). With *(3d)* and *(5e)*, the intensity of the signal at τ 5.89 is reduced to 1/2 and 3/4, respectively, thus this signal is securely assigned to the protons at C-1, C-3, C-4, and C-6. Quenching the above superacid solutions obtained from *(3c)* and *(5d)* with methanol containing excess sodium methoxide or carbonate at -78 °C provided *(5f)* in more than 80% yield as the sole isolable product. Therefore, we formulate the cation observed at -110 °C as *(4a)*, subject to the limitation of the NMR time scale. This cation was found to be thermally labile and warming the above solutions to -80 °C brought about an irreversible rearrangement, as evidenced by the appearance of a new set of NMR signals [(TMS, external) ^{1}H-NMR: τ 7.50 (2H/d, J = 13Hz), 6.56 (1H/s), 6.13 (2H/d, J = 13Hz), 5.56 (1H/t, $J \approx$ 4Hz), 3.52 (2H/br.s), -1.09 (1H/br.s); ^{13}C-NMR: δ_{TMS} 42.3, 46.3, 86.1, 111.4, 258.3] with some ill-defined background signals due to polymeric materials. Quenching (CH_3OH—Na_2CO_3, *vide supra*) of these solutions after the warming (-80 to -40 °C) afforded 3-methoxytricyclo[2.2.1.$0^{2,6}$]heptane *(6a)*[11] in *ca.* 50% yield. The NMR signals of the corresponding bromide *(6b)* in SbF_5—SO_2ClF at -50 °C were indeed superimposable on those described above. These results permit one to assign structure *(7)* to the rearranged cation. The pathway leading to *(7)* from *(4a)* appears unexceptional.

The ^{13}C-NMR spectrum of *(4a)* is presumably comparable to that reported by *Hart* and *Kuzuya*[12], yet the high-field ^{13}C absorption (δ -17.15) due to the apical

carbon demands comment. We have previously noted that increasing strain causes an upfield ^{13}C chemical shift. Examination of spectra of several tricyclo compounds such as *(5a)*, *(3a)*, *(6a)* and tricyclo[2.2.0.0^{2,6}]hexane *(8)* shows that the highest signals appear in the range δ 15—20 ppm, *i.e. ca.* 30—40 ppm lower than that due to C-7 of *(4a)*. This definitely suggests that the s,p-hybridization of the carbon bonding orbitals is unique and further that only a minimal positive charge resides at this carbon. Although the choice between the single cation *(4a)* or an equilibrating pair of *(4b)* and *(4c)* remains to be made, other theoretical and experimental results presently accumulating tend to place a slight preference for *(4a)* rather than *(4b)* and *(4c)* as the particular species obtained in superacid media[13].

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[2] *S. Masamune, R. Vukov, M. J. Bennett,* and *J. T. Purdham,* J. Amer. Chem. Soc. *94*, 8239 (1972). Related works were more recently reported: *P. G. Gassman* and *X. Creary,* J. Amer. Chem. Soc. *95*, 2729 (1973).

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[5] The C-4 proton of *(5a)* and *(5b)* appears at τ 5.66 and 4.62 ($CDCl_3$), respectively. The intensity of these signals were compared with those in the aromatic region. *(5a)* was converted to *(5b)* for this analytical purpose.

[6] *J. B. Stothers, C. T. Tan, A. Nickon, F. Huang, R. Sridhar,* and *R. Weglein,* J. Amer. Chem. Soc. *94*, 8581 (1972); *D. H. Hunter, A. L. Johnson, J. B. Stothers, A. Nickon, J. L. Lambert,* and *D. F. Corey,* J. Amer. Chem. Soc. *94*, 8583 (1972). The assignment to C-2 and C-7 may be reversed.

[7] *R. K. Lustgarten,* J. Amer. Chem. Soc. *94*, 7602 (1972).

[8] For a recent review on long-lived carbocations, see: *G. A. Olah,* Angew. Chem. internat. Edit. *12*, 173 (1973).

[9] Attempts to generate *(4a)* from the hydroxy and methoxy derivatives corresponding to *(3c)* and *(5d)* apparently led to the protonation of the cyclopropane ring as well as the hydroxy group and resulted in entirely different cations.

[10] The numbering of *(4a)* is arbitrary.

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[13] Solvolytic (trifluoromethanesulfonate) and deamination studies of *(9)* showed no indication of double bond participation. Cf. *W. Kirmse* and *F. Scheidt,* Angew. Chem. internat. Edit. *10*, 263 (1971).

New Cryptates Containing Tricyclic Ligands: Crystal Structure of $C_{32}H_{64}N_4O_{10} \cdot 2NaI$

By *Michel Mellinger, Jean Fischer,* and *Raymond Weiss*[*]

In solution the macrocycle *(1)* forms inclusion complexes of the [3]-cryptate type, *e.g.* with sodium iodide it forms the 1:2 complex *(1)*·2NaI[11].

This compound crystallizes in space group $P2_1/c$ with $a = 8.726(4)$, $b = 10.114(7)$, $c = 24.422(11)$ Å, $\beta = 103.89(4)°$, $d_{exp} = 1.52 \pm 0.05$, $d_{calc} = 1.530$ g/cm^3 and $Z = 2$.

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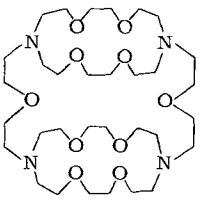
The intensities of the X-ray reflections were measured for a spherical crystal of diameter 0.3 mm with Mo—K_α-radiation on a Picker-FACS(I) single crystal diffractometer.



(1) = $C_{32}H_{64}N_4O_{10}$

2304 independent reflections with $\sigma(I)/I < 3\sigma$ were used for the structure analysis. At present the R value amounts to 0.069.

Figure 1 shows the structure of the complex dication of *(1)*·2NaI, which has a crystallographic center of symmetry. Two sodium ions are accommodated inside the tricyclic ligand, each of them being bonded to two nitrogen and five oxygen atoms of *(1)*.

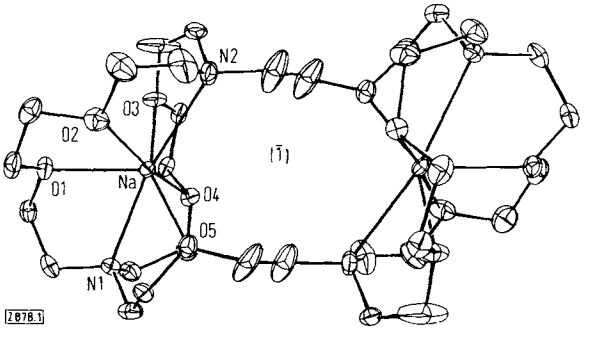


Fig. 1. Crystal structure of the complex dication of the inclusion compound *(1)*·2NaI.

The distances from Na^+ to N1 and N2 are 2.70(1) and 2.71(1) Å, respectively, and to O1, O2, O3, O4 and O5, vary between 2.39(1) and 2.48(1) Å. Similar values were found for the [2]-cryptate (222)·NaI and for the complex sodium salts with cyclic polyethers[2, 3].

The iodide ions no longer interact with the sodium ions: all the $Na^+ \cdots I^-$ separations exceed 5 Å. The distance between the two sodium ions in one ligand is 6.40 Å.

The determination of this structure confirms the finding that the tricyclic ligand *(1)* can enclose two metal cations. The two holes in this molecule have approximately the same diameter as in the bicyclic ligand (222) of the [2]-cryptate (222)·NaI, which has proved very stable[2].

The stability of the [3]-cryptate and the selectivity of the tricyclic ligand are less marked than for the [2]-cryptate and the bicyclic ligand, respectively[4]. This is probably due mainly to greater flexibility of the tricycle.

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[4] *J. Cheney, J. M. Lehn, J. P. Sauvage,* and *M. E. Stubbs,* J. C. S. Chem. Comm. *1972*, 1100.

Thermolysis of Tetramethyl-1,2-dioxetane

By *Peter Lechtken* and *Günther Höhne*[*]

Dedicated to Professor Gerhard Hesse on the occasion of his 65th birthday

A 1,2-dioxetane grouping has been recognized as the active intermediate formed during the course of many bioluminescent reactions[1]. Light emission from a biological or chemical system at room temperature is, however, possible only if one of the individual steps in the reaction chain liberates sufficient energy (as reaction enthalpy) to raise a product or acceptor molecule to the electronically excited state. The sum of the activation energy (E_A) and the reaction enthalpy (ΔH_R) must be at least as great as the energy of the photon radiated. At least 75 kcal are necessary for pale blue luminescence ($\lambda \approx 420$ nm).

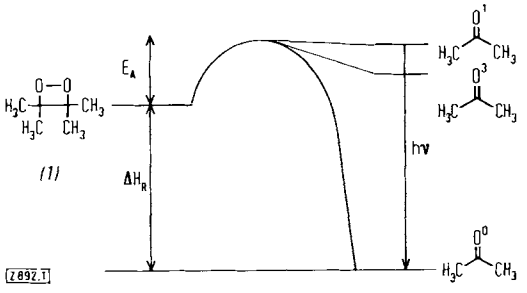

Fig. 1. Energy scheme for decomposition of tetramethyl-1,2-dioxetane *(1)* to acetone with chemiluminescence ($h\nu \approx 84$ kcal).

Tetramethyl-1,2-dioxetane *(1)*, which decomposes only slowly at room temperature, serves us as model for biogenic intermediates. Thorough investigation of the thermal fragmentation[2] in solution had shown that electronically excited acetone is formed from *(1)* in high yield, in which process the non-luminescent but energetically lower-lying triplet state[3] is favored 100-fold over the singlet state (Fig. 1). An attempted rationalization invokes a pericyclic scission[4] mechanism, but this is meaningful only if sufficient energy is available to make singlet or triplet formation equally probable. Several calculations indicate that between 60 and 100 kcal/mol should be liberated on fission of substituted dioxetanes[5].

We have now measured calorimetrically the reaction enthalpy of the thermolysis of *(1)* in the solid state and in solution. As an independent control we determined also the heat of combustion (Table 1).

Thermolysis of solid (1): A few mg of *(1)* were sealed in a cylindrical, air-tight, pressure-resistant, aluminum sample-holder (volume 90 mm³) and were then decomposed in a DSC calorimeter[6a] at a constant heating rate. Figure 2 shows the change in heat flow with temperature; the area under the curve is a measure of heat evolved. We find $Q_I = -68 \pm 3$ kcal/mol.

This value proved independent of the weight of the sample and of the rate of heating. If the rate of heating is the same, the plots of the thermograms are superposable if normalized for the weight of sample. If the rate of heating is lowered, the maximum of the decomposition is shifted,

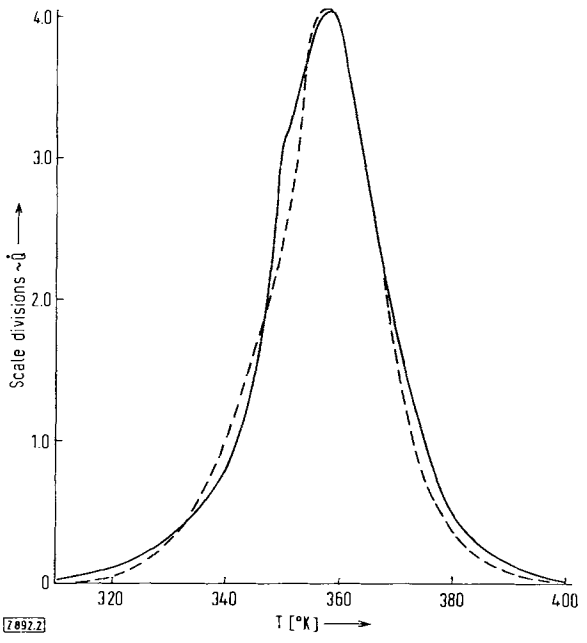

Fig. 2. Normalized thermogram of the decomposition of solid *(1)* (——) (curve I) and of *(1)* in dibutyl phthalate solution (– – –) (curve II). Rate of heating 5 deg/min.

as expected, to lower temperatures. Under these conditions *(1)* shows a melting point at *ca.* 343 K; the heat of melting can be crudely estimated as 1.5—2 kcal/mol.

Since the measurements were at constant volume, Q_I represents the internal energy ΔU, which must be recalculated into the enthalpy ΔH_I. Further a part of the heat of melting and of the heat of evaporation of acetone are included and corrections must be made appropriately[7].

Table 1. Reaction enthalpies in thermolysis of *(1)*.

Heat of reaction [kcal/mol]		No. of expts.	Change
ΔH_I	$= -71 \pm 3$	7	$(1)_{solid} \rightarrow acetone_{liq.}$
ΔH_{II}	$= -61 \pm 3$	7	$(1)_{soln.} \rightarrow acetone_{soln.}$
ΔH_{III}	$= -68 \pm 10$	2	$(1)_{solid} \rightarrow acetone_{liq.}$
ΔH_S	$= +1.8 \pm 0.3$	7	$(1)_{solid} \rightarrow (1)_{liq.}$
$\Delta H_{combstn.}$	$= -922 \pm 10$	2	combustion

Thermolysis of dissolved (1): About 3 mg of *(1)* are dissolved in *ca.* 50 mg of dibutyl phthalate and decomposed under conditions similar to those above. The value ΔH_{II} still contains the solvation energies of *(1)* and of acetone in dibutyl phthalate. For the lower exothermicity found, we have as yet no satisfactory explanation, and it is under further investigation.

Combustion in a Berthelot bomb: 60 mg samples of *(1)* were burnt in an adiabatic combustion calorimeter[6b] under 15 atm of O_2. The extremely violent reaction gave $\Delta U_{combstn.} = -920 \pm 10$ kcal/mol, which corresponds to $\Delta H_{combstn.} = -922$ kcal/mol. After taking into account the heat of combustion of acetone ($\Delta H = -426.7$ kcal/mol) we reach the value $\Delta H_{III} = -68 \pm 10$ kcal/mol.

Thus about 70 kcal/mol are liberated on cleavage of *(1)* in the solid state into two molecules of acetone, and 61 kcal/mol in solution. Adding the activation energy of decomposition in solution $E_A = 25$ kcal/mol[4], we find

$E_A + H_R = 86$ kcal/mol

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at our disposal, which is just enough to produce either singlet ($E^S_{acetone} = 84$ kcal/mol) or triplet acetone ($E^T_{acetone} = 78$ kcal/mol). This accords with recent results that after taking up enough activation energy to yield an "activated complex", *(1)* needs no further addition of energy to form singlet or triplet acetone[9]. Our results now to hand indicate, however, that it may be possible to obtain considerably more luminescent singlet acetone on decomposition of *(1)* in the vapor phase than is possible in solution.

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[6] a) DSC calorimeter, type CPC 600, Arion, Grenoble; b) combustion calorimeter, Peters KG, Berlin 21.

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Direct Observation of the Dissociation Equilibrium of Tropylium Salts[**]

By *Horst Kessler* and *Axel Walter*[*]

Dedicated to Professor Karl Winnacker on the occasion of his 70th birthday

Mechanistic studies of the S_N1 reaction have shown that dissociation to "free" carbenium ions occurs by way of an intimate ion pair and a solvent-separated ion pair, and that a steady state concentration of cations is established[1]. The definition of intermediates makes sense only if such species are separated by an energy barrier[2]. Ions (ion pairs) and nonionic molecules should be observable alongside each other by NMR spectroscopy if the time scale of the detection method[3] permits their detection and if their free energies are comparable. Hitherto, to the best of our knowledge, dissociable compounds have been observed either in nonionic or in dissociated form, but not side by side.

We have found a tropylium salt that exists in solution in dissociated and undissociated forms together, these forms being separated by relatively high energy barriers. The NMR spectrum of cycloheptatrienyl isothiocyanate *(1)*[4] in $CDCl_3$ or ether at -40 °C is the usual one for 7-substituted cycloheptatrienes [$\delta = 6.8$ (t, 3-H, 4-H), 6.4 (m, 2-H, 5-H), 5.6 (dd, 1-H, 6-H), and 4.1 (t, 7-H, $J = 5$ Hz)], but when the temperature is raised to *ca.* $+20$ °C it is reversibly broadened and all the signals coalesce, indicating migration of the NCS group around the whole seven-membered ring[5]. In acetonitrile, *(1)* dissolves only as tropylium isothiocyanate (singlet at $\delta = 9.2$), but surprisingly both forms are observed together in $CD_3CN/CDCl_3$ (1:3) at -40 °C (Fig. 1).

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[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

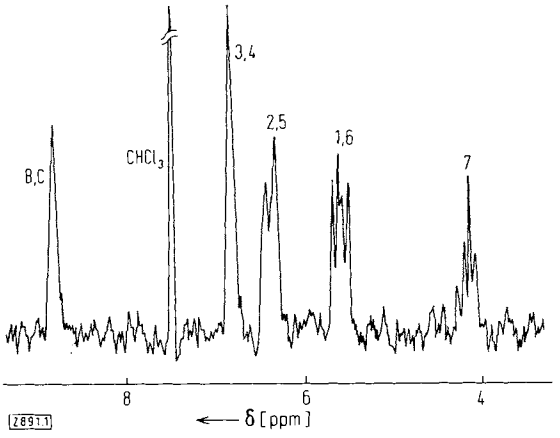
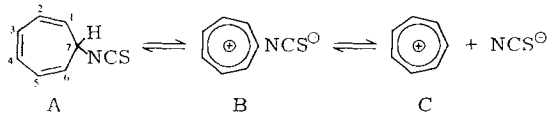


Fig. 1. ^{1}H-NMR spectrum of tropylium isothiocyanate in $CD_3CN/CDCl_3$ (1:3) at -40 °C; B, C: forms B and C of *(1)*; numerals are numbers of H atoms in A.



A B C

(1)

The equilibrium between the ionized form (B, C) and the nonionized form (A) was demonstrated by irradiation at the tropylium frequency at -15 °C, which led to saturation of the whole cycloheptatriene spectrum[7].

The intensity ratio of A:(B,C) can be modified by addition of tropylium tetrafluoroborate or by change in the composition of the solvent, but not by alteration of the concentration of the solute in the solvent mixture. The tropylium salt must therefore exist in this solvent mixture preponderantly as ion pairs B. With increasing amount of chloroform in the (originally pure) acetonitrile solvent, the position of the tropylium signal shifts to higher field and thus indicates increasing pairing of the ions. This also follows from the kinetics. Broadening of the tropylium signal in the solvent mixture is independent of the concentration (first-order reaction; $\Delta G^{\ddagger}_{243} = 12$ kcal/mol[8]). The barrier thus lies between the ion pair B and the cycloheptatriene A. A possible reason for its size may perhaps be seen in the aromatic tropylium system which has to be distorted on approach of the anion[10].

Tropylium halides cannot be dissolved in apolar solvents at concentrations detectable by NMR spectroscopy: in acetonitrile only the dissociated form can be detected. On the other hand, 7-cyanocycloheptatriene exists completely undissociated and there is no migration of the cyanide group. Nevertheless, equilibria between 7-substituted cycloheptatriene and their corresponding ions were observed, just as for the isothiocyanate, with the anions $N_3^{\ominus}$, $ONO^{\ominus}$, and $NCO^{\ominus}$[12]. Therefore those anions represent an intermediate position and permit a study of ion recombinations[13] that will contribute to our understanding of the S_N1 mechanism. The migration of these anions around the cycloheptatriene ring can therefore be explained by ionization. To what extent other mechanisms (*e. g.* [1,5]- or [3,3]-sigmatropic shifts) are involved remains to be investigated.

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[1] *R. A. Sneen*, Accounts Chem. Res. 6, 46 (1973), and literature cited therein.

[2] *R. Huisgen*, Angew. Chem. *82*, 783 (1970); Angew. Chem. internat. Edit. *9*, 751 (1970).

[3] *H. Kessler*, Angew. Chem. *82*, 237 (1970); Angew. Chem. internat. Edit. *9*, 219 (1970).

[4] Prepared by reaction of tropylium tetrafluoroborate with sodium thiocyanate. The IR spectrum of its ethereal solution shows a strong band at 2060 cm^{-1} characteristic of R—NCS compounds.

[5] The same effect was observed previously with tropylium azide [6].

[6] *D. S. Wulfman, L. Durham*, and *C. E. Wulfman*, Chem. Ind. (London) *1962*, 859.

[7] *R. A. Hoffman* and *S. Forsén*, Progr. NMR Spectrosc. *1*, 15 (1966).

[8] Determined from the broadening of the tropylium signal according to the approximation $k=\pi b_A$ (b_A = line broadening by exchange) [9].

[9] *I. O. Sutherland*, Annu. Rep. NMR Spectrosc. *4*, 71 (1971).

[10] A high barrier was also observed for dissociation of Meisenheimer complexes [11]. These also correspond to the system: aromatic compound $+X^-$.

[11] *P. Caveng* and *H. Zollinger*, Helv. Chim. Acta *50*, 861 (1967).

[12] Solvent: $SO_2/CDCl_3$ for $N_3^{\ominus}$, CD_3CN for $ONO^{\ominus}$ and $NCO^{\ominus}$.

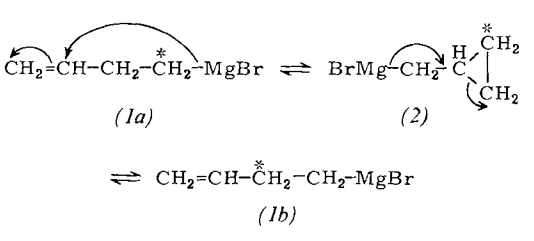
[13] *C. D. Ritchie*, Accounts Chem. Res. *5*, 348 (1972).

Influences of α- and β-Alkyl Groups on the Rearrangement of 3-Butenyl Grignard Reagents: A Stable Primary Cyclopropylmethyl Anion[**]

By *Adalbert Maercker, Paul Güthlein*, and *Hermann Wittmayr*[*]

Dedicated to Professor Gerhard Hesse on the occasion of his 65th birthday

By isotopic labeling experiments *Roberts et al.*[1] demonstrated that the α- and β-carbon atoms of 3-butenyl Grignard reagents gradually interchange positions: *(1a)*⇌*(1b)* (half-reaction time *ca.* 30 h at 27 °C). A cyclopropylmethyl Grignard reagent *(2)* is assumed as an intermediate but its presence in the equilibrium mixture could not be detected. If *(2)* is prepared at low temperatures by an independent route, it rearranges quantitatively to *(1)* already at −24 °C with a half-reaction time of 2 h[2]. The reason for this is the large ring strain in the cyclopropane (27 kcal/mol), which also explains why *(2)* cannot be detected in the equilibrium *(1a)*⇌*(2)*⇌*(1b)*: the energy difference between *(1)* and *(2)* was estimated to be 7 kcal/mol[2].



(1a) *(2)*

$\rightleftharpoons CH_2{=}CH{-}\overset{*}{C}H_2{-}CH_2{-}MgBr$

(1b)

The energy difference between *(2)* and *(1)* can in principle be reduced by stabilizing the three-membered ring of *(2)* or by destabilizing the 3-butenyl Grignard reagent *(1)*. The best chance of success lies in the combination of these two possibilities.

We hoped to stabilize the cyclopropane ring by introducing geminal alkyl groups (Thorpe-Ingold effect)[3-6].

A possible method of destabilizing the open-chain Grignard reagent *(1)* appeared to be the introduction of alkyl groups on the α-carbon atom, *i.e.* at the carbanionic center (cf. Ref. [7]).

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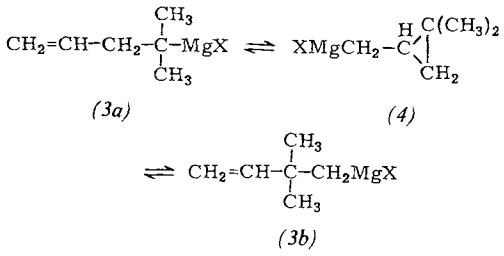
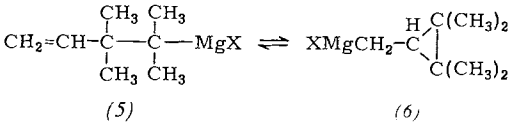
[**] This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.



(3a) *(4)*

(3b)

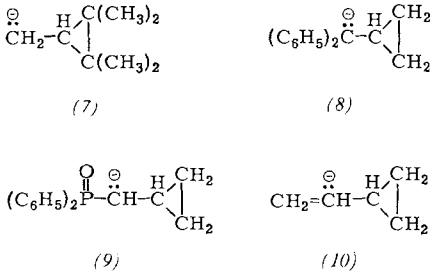
Investigation of the rearrangement *(3a)*⇌*(4)*⇌*(3b)* with X = Cl in tetrahydrofuran was only partly successful. Certainly the tertiary Grignard reagent *(3a)* rearranges quantitatively (half-reaction time *ca.* 30 h at 70 °C) and the cyclopropylmethyl compound *(4)* (*ca.* 0.07%) can be unambiguously detected but the equilibrium lies more than 99.9% on the side of the primary 3-butenyl Grignard reagent *(3b)* (determined by gas chromatography after esterification of the carboxylation products by diazomethane). Thence it follows that the two geminal methyl groups do in fact powerfully stabilize the three-membered ring, yet the Thorpe-Ingold effect alone does not suffice to shift the equilibrium in favor of the cyclopropylmethyl compound *(4)*.



(5) *(6)*

Complete success, however, followed introduction of four methyl groups. In the equilibrium mixture *(5)*⇌*(6)* (X = Cl) there is only *one* open-chain compound since the α- and the β-carbon atoms are equally substituted. This tertiary Grignard reagent *(5)* rearranges already at room temperature in tetrahydrofuran (concn. 0.04—0.4 mol/l) to give more than 99.9% of the cyclic compound *(6)* which, unlike *(4)*, cannot pass into a primary 3-butenyl Grignard reagent by ring opening.

In *(6)*, which is also accessible directly from *(6)* with Cl in place of ClMg, we have the first completely stable *primary* cyclopropylmethyl Grignard reagent [^{1}H-NMR: α-methylene doublet at $\tau = 10.9$ ($J = 7$ Hz)]. Except for the 2,2,3,3-tetramethylcyclopropylmethyl anion *(7)*, all the stable cyclopropylmethyl anions previously known were substituted at the carbanionic center, *e.g.* the benzhydryl *(8)*[8], the phosphane oxide *(9)*[9] and the vinyl anion *(10)*[10].



(7) *(8)*

(9) *(10)*

Kinetic measurements (NMR and gas chromatography) gave a half-reaction time of *ca.* 6 h for the equilibration *(5)*⇌*(6)* at 23 °C, so the rearrangement is appreciably faster than that of *(3a)*. Remarkable also is that preparation of *(5)* and *(6)* is possible only when X = Cl. Reaction

of the bromo compounds with magnesium in either diethyl ether or tetrahydrofuran gave no trace of the Grignard compound, but exclusively disproportionation products, and these—unlike the anion case—from the clearly more stable *open-chain* radical. The complete absence of cyclopropane derivatives from the products of radical reaction, even if cyclopropylmethyl bromide is used as starting material, is a further indication of the carbanionic nature of these Grignard rearrangements[11].

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German version: Angew. Chem. 85, 823 (1973)

[1] *M. S. Silver, P. R. Shafer, J. E. Nordlander, C. Rüchardt,* and *J. D. Roberts,* J. Amer. Chem. Soc. *82*, 2646 (1960).

[2] *D. J. Patel, C. L. Hamilton,* and *J. D. Roberts,* J. Amer. Chem. Soc. *87*, 5144 (1965).

[3] *R. M. Beesley, C. K. Ingold,* and *J. F. Thorpe,* J. Chem. Soc. *107*, 1080 (1915); *C. K. Ingold, ibid. 119*, 305, 951 (1921); *G. A. R. Kon, A. Stevenson,* and *J. F. Thorpe, ibid. 121*, 650 (1922).

[4] Cf. *N. L. Allinger* and *V. Zalkow,* J. Org. Chem. *25*, 701 (1960).

[5] *J.-M. André, M.-C. André,* and *G. Leroy,* Bull. Soc. Chim. Belges *80*, 265 (1971).

[6] *W. D. Good,* J. Chem. Thermodyn. *3*, 539 (1971).

[7] *A. Maercker* and *R. Geuss,* Chem. Ber. *106*, 773 (1973).

[8] *A. Maercker* and *J. D. Roberts,* J. Amer. Chem. Soc. *88*, 1742 (1966).

[9] *A. Maercker,* Angew. Chem. *79*, 576 (1967); Angew. Chem. internat. Edit. *6*, 557 (1967).

[10] *H. G. Richey, Jr.* and *W. C. Kossa, Jr.,* Tetrahedron Lett. *1969*, 2313; cf. also *M. Santelli* and *M. Bertrand,* C. R. Acad. Sci. *C 271*, 757 (1970).

[11] Cf. *A. Maercker* and *W. Streit,* Angew. Chem. *84*, 531 (1972); Angew. Chem. internat. Edit. *11*, 542 (1972).

New Aspects of the Fries Rearrangement[1]

By *Franz Effenberger, Herbert Klenk,* and *Peter Ludwig Reiter*[*]

Dedicated to Professor Karl Winnacker on the occasion of his 70th birthday

Even in the most recent literature, the Fries rearrangement of phenolic esters *(1)* not substituted in the arene nucleus (R = R' = H) is held to be an irreversible process yielding *o*- and/or *p*-hydroxyaryl ketones (acylphenols)[2]. *Rosenmund* and *Schnurr*[3] as well as *Miguel et al.*[4] have reported a reversal of the Fries rearrangement for 4-acyl-3-alkylphenols whereas *Cullinane* and *Edwards*[5] maintain that the Fries rearrangement is irreversible in this case too.

Formerly we had found that aromatic compounds can be acylated by acyl chlorides or carboxylic anhydrides under the influence of catalytic amounts of trifluoromethanesulfonic acid (TFMS)[6]. Since *C*-acylation of phenols is of great practical importance, we have investigated whether the Fries rearrangement which is usually carried out with molar amounts of $AlCl_3$ could also be achieved with TFMS-catalysis.

If solutions of phenyl benzoates *(1)* in anhydrous tetrachloroethane are heated with *ca.* 2 mol-% TFMS for 24 h at 170 °C in sealed tubes, the reaction mixture contains *o*-hydroxyaryl ketones *(2)*, phenols *(3)*, and decomposition products besides starting material (Table 1).

Reactions run on a preparative scale (*e.g.* 0.1 mol *(1a)*, 0.02 ml TFMS in 100 ml anhydrous tetrachloroethane) give

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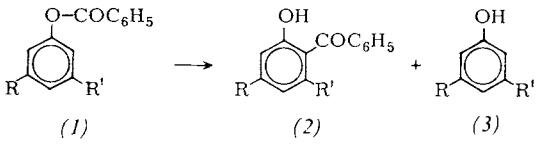


(1) *(2)* *(3)*

Table 1. Fries rearrangement of phenyl benzoates *(1)* with catalytic amounts of trifluoromethanesulfonic acid.

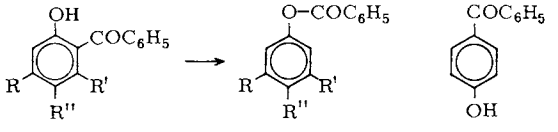
Starting material	R	R'	Products [%] [a] *(1)*	*(2)* [b]	*(3)*	decomp. products
(1a)	H	H	48	39	5	8
(1b)	H	NO_2	100	—	—	—
(1c)	H	CH_3	40	49	11	—
(1d)	H	CH_3O	7	78	—	15
(1e)	CH_3	CH_3	100	—	—	—

[a] Average yields from several parallel runs, determined by glc (Varian 1200).
[b] *p*-Hydroxyaryl ketones are formed in less than 2% yield, if at all.

yields identical within the error limit with those in Table 1. Phenolic esters of aliphatic carboxylic acids also undergo Fries rearrangement with TFMS.

Electron donors in position 3 of the phenolic ester favor the TFMS-catalyzed rearrangement as the results in Table 1 indicate: starting from *(1d)*, *(2d)* was obtained in 78% yield while *(1b)* remained unchanged under the reaction conditions. Surprisingly, *(1e)* did not rearrange even though the two methyl groups at C-3 and C-5 should enhance acylation of the arene nucleus. This finding can be rationalized in terms of reversibility of the Fries rearrangement.

In order to test this hypothesis, we have heated several *o*-hydroxyaryl ketones with TFMS under the conditions given above. These experiments (Table 2) clearly show the Fries rearrangement to be indeed reversible.



(2) *(1)* *(4)*

Table 2. Retro Fries rearrangement of *o*-hydroxyaryl ketones *(2)* with catalytic amounts of TFMS.

Starting material	R	R'	R''	Products [%] [a] *(2)*	*(1)*	decomp. products
(2a)	H	H	H	75	25	—
(2e)	CH_3	CH_3	H	—	90	10
(2f)	H	H	CH_3	47	53	—
(4)				*(4)*, 23 *(2a)*, 9	*(1a)*, 40	28

[a] See note [a] in Table 1.

There is qualitative agreement between the isomer distribution for the Fries and the retro Fries rearrangement (Table 1 *vs.* Table 2); this is not sufficient, however, to establish a truly reversible equilibrium (which should be attained from either direction) so that further investigations are necessary.

The mechanisms proposed so far for the Fries rearrangement must now be critically reviewed since they do not take account of the reversibility of the reaction which has been established beyond doubt by the results reported here, especially since we have found the retro rearrangement also with typical Friedel-Crafts catalysts such as $FeCl_3$.

Our inference from the experimental data given is that for the acid-catalyzed Fries rearrangement product formation is subject to thermodynamic control in many cases. Since phenolic esters and hydroxyaryl ketones seem to have about the same energy they are present side by side in solution. Steric hindrance due to buttressing of two *o*-substituents as in *(2e)* shifts the isomer distribution in favor of the sterically unhindered ester (Table 2). We observe almost exclusive *o*-rearrangement which is another argument in favor of the thermodynamic control mechanism since the *o*-hydroxyaryl ketones are stabilized by intramolecular hydrogen bonding which is impossible in the *p*-isomers.

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German version: Angew. Chem. *85*, 819 (1973)

[1] Electrophilic Substitution of Aromatic Compounds, Part 8.—Part 7: *F. Effenberger* and *H. Klenk*, Chem. Ber., in press.—We are indebted to the Fonds der Chemischen Industrie and the Deutsche Forschungsgemeinschaft for support of this work.

[2] *M. J. S. Dewar* and *L. S. Hart*, Tetrahedron *26*, 973 (1970).

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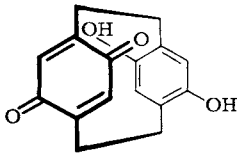
[5] *N. M. Cullinane* and *B. F. R. Edwards*, J. Chem. Soc. *1958*, 434.

[6] *F. Effenberger* and *G. Epple*, Angew. Chem. *84*, 295 (1972); Angew. Chem. internat. Edit. *11*, 300 (1972).

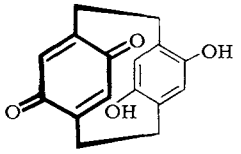
An "Intramolecular Quinhydrone"[1]

By *Walter Rebafka* and *Heinz A. Staab*[*]

In the context of our investigations of transannular interactions in [2.2]phanes[1,2] we became interested in compounds where high electron affinity in one part of the molecule and low ionization energy in the other favor intramolecular donor-acceptor interactions. Ideal conditions for this interaction should be provided by "intramolecular quinhydrones"[3] in the [2.2]paracyclophane series, for which pseudoortho- and pseudogeminal stereoisomers *(1a)* and *(1b)* can be foreseen. We report here the synthesis of *(1a)*[4].

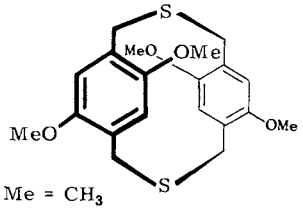


(1a)

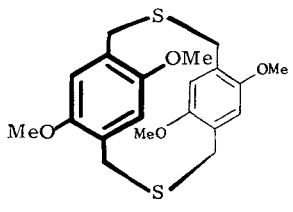


(1b)

1,4-Bis(bromomethyl)-2,5-dimethoxybenzene (0.1 M in tetrahydrofuran) and 1,4-bis(mercaptomethyl)-2,5-dimethoxybenzene (0.1 M in dimethylformamide) were cyclized by being dropped simultaneously into a suspension of anhydrous potassium carbonate (excess) in boiling tetrahydrofuran/dimethylformamide (1:1) (for apparatus see Ref. [5]), thus yielding 5,8,14,17-tetramethoxy-2,11-dithia[3.3]paracyclophane *(2a/2b)* in 20—23% yield. Chromatographic separation from chloroform on silica gel yielded the two stereoisomers of m.p. 211—213 °C and 243—246 °C[6] in the ratio *ca.* 2:1; assignment of the two compounds to the chiral *(2a)* and the achiral *(2b)* forms has not yet been unambiguously effected.

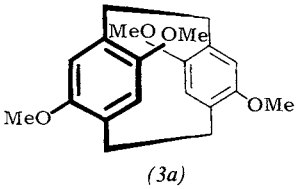


(2a)

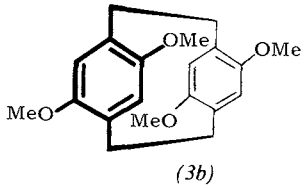


(2b)

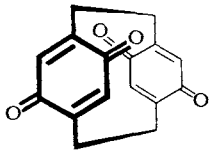
Ring contraction to give 4,7,12,15-tetramethoxy[2.2]paracyclophane *(3a)* or *(3b)* has been achieved in three ways: first, by gas-phase pyrolysis (440 °C/10^{-3} torr, 30—45% yield) of the disulfones obtained (H_2O_2, chloroform/glacial acetic acid, ≈70% yield) from *(2a)* and *(2b)* or the *(2a)/(2b)* mixture; secondly, by photolysis of the disulfones (suspension in benzene, Hg high-pressure lamp, 75 min, 50% yield); and thirdly, by direct photolytic desulfuration of *(2a)/(2b)* in triethyl phosphite in a modification of a procedure due to *Bruhin* and *Jenny*[7]. Independently of whether the starting material was *(2a)*, *(2b)* or the *(2a)/(2b)* mixture, by each of these ring contraction reactions only *one* product was obtained [m.p. 121—122 °C; ^{1}H-NMR ($CDCl_3$): τ = 3.91 (s, 4 arom. H), 6.34 (s, 12 methoxy-H), 7.6—6.6 (AA'BB', 8 methylene-H)][6]. The decision between *(3a)* and *(3b)* was established in favor of the chiral *(3a)* since partial separation of the enantiomers was effected by chromatography on (−)-2-(2,4,5,7-tetranitro-9-fluorenylideneaminooxy)propionic acid ["(−)-TAPA"; 10%]/silica gel from cyclohexane/methylene chloride (3:1): the maximum rotations were $[\alpha]_{365}^{28°} = +17.8°$ (1.03 g/100 ml; $CHCl_3$) and −18.0° (0.4 g/100 ml; $CHCl_3$); (−)-*(3a)* formed the more stable complex with (−)-TAPA. The subsequent products from *(3a)* very probably also have the pseudoortho conformation.



(3a)



(3b)



(4)

Demethylation of *(3a)* could only be achieved by heating with methylmagnesium iodide (15 min, 170—185 °C, under N_2)[8]. Without being purified, the resulting rather unstable tetrahydroxy[2.2]paracyclophane was oxidized by sodium periodate in tetrahydrofuran (20 °C, 40—60 min) to the bis-quinone *(4)* [yield *(3a)*→*(4)* ≈50%] which formed yellow crystals decomposing above 200 °C. ^{1}H-NMR

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($CDCl_3$): $\tau = 7.8$—6.5 (m, 8 methylene-H), 3.70 (d, 4 arom. H; $J \approx 0.9$ Hz); MS: M^+ 268 (base peak); the fragmentation corresponds essentially to that of simple *p*-benzoquinones (no fragmentation into halves as for true [2.2]paracyclophanes); IR (KBr): 1660 cm^{-1} s.

Catalytic hydrogenation of *(4)* (Pd/C, dioxane, calculated amount of H_2) and subsequent chromatography (silica gel, from ether/chloroform) and recrystallization from benzene/ether gave the intramolecular quinhydrone *(1a)*[6] in 70% yield. Mass spectrum: M^+ found 270.0868, calc. 270.0891; ^{1}H-NMR ([D_6]-acetone): $\tau = 7.8$—6.5 (m, 8 methylene-H), 3.95 (s, 2H), 3.80 (s, 2H), 2.22 [s, 2H (OH, concentration-dependent, exchange with D_2O and CD_3OD)]; IR (KBr): $\nu OH = 3420\,cm^{-1}$, $\nu CO = 1645\,cm^{-1}$.

In contrast to the quinhydrones, which dissociate partially in solution, the dark violet crystals of *(1a)* form wine-red solutions in polar solvents. The absorption spectrum of *(1a)* in methanol has an extremely broad absorption band ($\lambda_{max} = 515$ nm, $\varepsilon = 170$), stretching on the long-wave side far above 600 nm.

In solution, *(1a)* is oxidized to *(4)* by atmospheric oxygen. We failed in attempts to detect rapid interchange of oxidation states between the two rings, involving hydrogen transfer, which would have been shown by coalescence of the ^{1}H-NMR signals at $\tau = 3.95$ and 3.80, at temperatures up to 200 °C (in hexamethylphosphorotriamide). When treated with aqueous 0.1 N sodium hydroxide, the solution of *(1a)* in methanol changes from wine-red through green to reddish-brown, and this change is reversed by addition of the corresponding amount of 0.1 N hydrochloric acid. Presumably the dianion, which may exist as a diamagnetic donor-acceptor complex or, through complete electron transfer, as a double semiquinone radical anion, is formed through the monoanion stage.

Received: July 2, 1973 [Z 881 IE]
German version: Angew. Chem. *85*, 831 (1973)

[1] Transannular Interactions in [2.2]Phanes, Part 4. — Part 3: *M. Haenel* and *H. A. Staab*, Chem. Ber. *106*, 2203 (1973).

[2] *H. A. Staab* and *M. Haenel*, Chem. Ber. *106*, 2190 (1973); see also *M. Haenel* and *H. A. Staab*, Tetrahedron Lett. *1970*, 3585.

[3] We use this term because of its simplicity, although it contains a "contradictio in adiecto": quinhydrones are defined as dissociable complexes of quinonoid acceptor and benzenoid donor molecules, whereas in *(1a)* and *(1b)* the donor and the acceptor are contained in *one* molecule.

[4] *D. J. Cram* and *A. C. Day* [cf. J. Org. Chem. *31*, 1227 (1966)] started the synthesis of these "exotic quinhydrones" a considerable time ago, but apparently could not complete this work.

[5] *F. Vögtle*, Chem. Ind. (London) *1972*, 346.

[6] Correct elemental analyses were obtained for these compounds; ^{1}H-NMR and mass spectra, as well as other spectroscopic results, are in accordance with the structure proposed.

[7] *J. Bruhin* and *W. Jenny*, Tetrahedron Lett. *1973*, 1215.

[8] Cf. *M. S. Kharash* and *O. Reinmuth*. Grignard Reactions of Nonmetallic Substances. Prentice Hall, New York 1954, p. 1013.

Detection of Free Cyclobutadiene on Oxidation of a Tricarbonyl(cyclobutadiene)iron Complex

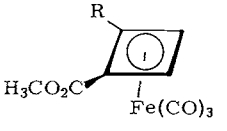
By *E. K. G. Schmidt*[*]

Dedicated to Professor Karl Winnacker on the occasion of his 70th birthday

Recent work has shown that unsubstituted cyclobutadiene has a finite lifetime only under extreme conditions, *e.g.* in a noble-gas matrix at 8 °K[1]. However, this molecule has been postulated as intermediate in a series of reactions[2a], and it has been credited with an astonishing selectivity in cycloadditions even at room temperature[2b].

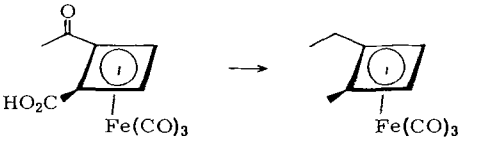
We have tested the possibilities that free cyclobutadiene is actually liberated on oxidative degradation of its tricarbonyliron complex[3] or alternatively that the molecule is still complexed during the observed additions to olefins. Earlier experiments had not led to conclusive results[4]. If the reaction of an optically active cyclobutadiene complex proceeds by way of free cyclobutadiene then racemic products are to be expected, but in other cases they should be optically active.

As a model compound we synthesized optically active tricarbonyl-(1-ethyl-2-methylcyclobutadiene)iron *(3)* as follows: Reaction of the half ester *(1a)*[5] with oxalyl chloride in pyridine led to *(1b)*, which with diazomethane afforded the diazo ketone *(1c)*. Treatment of *(1c)* with HI in acetic acid gave *(1d)* in overall yield of 72%[6].



(1a), R = CO_2H
(1b), R = COCl
(1c), R = $COCHN_2$
(1d), R = $COCH_3$

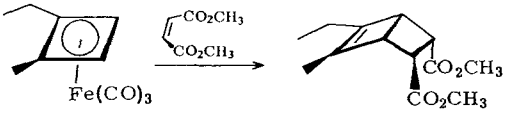
(1d) was hydrolyzed to the acid *(2)*, which was reduced by B_2H_6–BF_3 in THF to racemic *(3)* in 95% yield[7].



(2) *(3)*

Resolution of the acid by quinine afforded optically active (−)-*(2)*, $[\alpha]_{578}^{24} = -102°$ (in ethanol). Esterification with diazomethane gave (−)-*(1d)*, $[\alpha]_{578}^{24} = -280°$ (in benzene), whose optical purity (>99%) was determined by ^{1}H-NMR spectroscopy with the aid of a chiral europium complex[8]. Reduction of (−)-*(2)* gave (−)-*(3)*, $[\alpha]_{578}^{24} = -20.5°$ (in CCl_4), which should be of equal optical purity[9].

On oxidation of (−)-*(3)* in methanol at 0 °C by cerium(IV) ammonium nitrate in the presence of dimethyl maleate (37-fold excess) the diester *(4)* was obtained as sole adduct (40%)[10]. A 40% solution of the adduct in benzene, in a 10 cm cuvette, showed zero rotation (within the error of the polarimeter, ±0.003°) at 578 and at 435 nm. The presumption therefrom that *(4)* is obtained in its racemic form can be convincingly confirmed as follows: in the ^{1}H-NMR spectrum addition of the above shift reagent[8] causes splitting of the enantiotopic signals (ester-methyl, allylic methyl, and ethyl group) in the ratio 1:1 (accuracy of measurement 7%).



(-)-*(3)* *(4)*

On oxidative degradation of (−)-*(3)* in the presence of the more reactive dienophile maleic anhydride (two-fold

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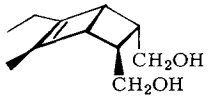
amount), again only one adduct was formed; this was reduced to the diol *(5)* by $LiAlH_4$ [40% yield referred to *(−)-(3)*[10]]. By the criteria used for *(4)*, this alcohol was also racemic. Even with the very reactive dienophile tetracyanoethylene we obtained the optically inactive adducts *(6)*, *(7)*, and *(8)* [50% based on *(−)-(3)*], of which the bicyclohexene *(6)* with two alkyl groups on the double bond is the favored product[11]. The regiospecificity observed with the less reactive dienophiles is thus lost in this Diels-Alder reaction[12].



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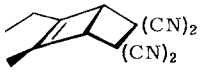
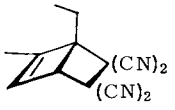
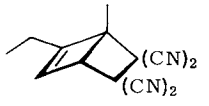


(6)



(7)



(8)

The formation of racemic adducts from the optically pure tricarbonyliron complex proves the occurrence of free cyclobutadiene. During addition of the dienophile, possible residual bonds from the cyclobutadiene to the iron or to the solvent are clearly too weak to maintain the original chiral surroundings of the complex.

Received: June 25, 1973 [Z 875 IE]
German version: Angew. Chem. 85, 820 (1973)

[1] *O. L. Chapman, D. DeLaCruz, R. Roth,* and *J. Pacansky,* J. Amer. Chem. Soc. *95,* 1337 (1973); *O. L. Chapman, C. L. McIntosh,* and *J. Pacansky, ibid. 95,* 616 (1973); *A. Krantz, C. Y. Lin,* and *M. D. Newton, ibid. 95,* 2744 (1973) and literature cited therein; *S. Masamune, M. Suda, H. Ona,* and *L. M. Leichter,* J. C. S. Chem. Commun. *1972,* 1268.

[2] a) *J. Font, S. C. Barton,* and *O. P. Strausz,* Chem. Commun. *1970,* 499; *R. Criegee* and *R. Huber,* Chem. Ber. *103,* 1862 (1970); *M. F. Semmelhack* and *R. J. DeFranco,* J. Amer. Chem. Soc. *94,* 8838 (1972); b) *L. Watts, J. D. Fitzpatrick,* and *R. Pettit, ibid. 88,* 623 (1966); *E. K. G. Schmidt, L. Brener,* and *R. Pettit, ibid. 92,* 3240 (1970), and literature cited therein.

[3] *R. Pettit,* Pure Appl. Chem. *17,* 253 (1968); *E. E. Nunn* and *R. Warrener,* J. C. S. Chem. Commun. *1972,* 818; *E. Vedejs, ibid. 1971,* 536; *L. A. Paquette* and *J. F. Kelly,* Tetrahedron Lett. *1969,* 4509.

[4] *W. J. R. Tyerman, M. Kato, P. Kebarle, S. Masamune, O. P. Strausz,* and *H. E. Gunning,* Chem. Commun. *1967,* 497; *L. Watts, J. D. Fitzpatrick,* and *R. Pettit,* J. Amer. Chem. Soc. *87,* 3253 (1965).

[5] *B. W. Roberts, A. Wissner,* and *R. A. Rimermann,* J. Amer. Chem. Soc. *91,* 6208 (1969).

[6] The new compounds were characterized by elemental analysis and ^{1}H-NMR, UV, and IR spectroscopy.

[7] Yellow liquid, b.p. 86 °C/7 torr. IR (CCl_4): 2970 w, 2039 vs, 1966 vs, 617 s, 590 s cm^{-1}. ^{1}H-NMR (C_6D_6): ring protons $\delta = 3.62$ ppm (s, 1H), 3.58 (s, 1H); methyl group 1.48 (s, 3H); ethyl group 1.82 (q, 2H), 0.87 (t, 3H, $J \approx 7.3$ Hz). Typical for tricarbonyl(cyclobutadiene) complexes is the absence of coupling between the ring protons and the diastereotopic splitting of the signals of the ethyl group [cf. *H. A. Brune, H. P. Wolff,* and *H. Hüther,* Tetrahedron *27,* 3949 (1971)]. The mass spectrum shows the molecular ion ($m/e = 234$), as well as the successive loss of three CO groups.

[8] Tris-[3-(heptafluoro-1-oxidobutylidene)-(+)camphorato]europium(III); Willow Brook Laboratories, Inc.; review: *H. L. Goering, J. N. Eikenberry,* and *G. S. Koermer,* J. Amer. Chem. Soc. *93,* 5913 (1971).

[9] *(−)-(3)* is thermally very stable; a sample was recovered unchanged after being heated in benzene for 50 h at 200 °C.

[10] Experiments with Eu shift reagents indicate the *endo*-configuration, but the validity of this assignment is of no importance for our work above.

[11] *(6)* and *(7)* were isolated in a state of purity, but *(8)* only in admixture with *(7)*.

[12] With less active dienophiles 1,2-diphenylcyclobutadiene also gave only one adduct, but with TCNE it gave two adducts: *P. Reeves, T. Devon,* and *R. Pettit,* J. Amer. Chem. Soc. *91,* 5890 (1969).

CONFERENCE REPORTS

Constitution of Nonstoichiometric Compounds and Solid Solutions

By *J. S. Anderson*[*]

Work of recent years has shown that the structure of nonstoichiometric solids cannot be explained only in terms of point defect vacancies or interstitials: the host structure is modified around a defect and a point defect is replaced by a defect complex. Alternatively, the modification may completely eliminate a sheet of lattice sites, by crystallographic shear.

Neutron diffraction has proved particularly suited to the determination of defect structure. Work on anion-excess fluorite type solid solutions has shown that these contain defect complexes of the same type as were proposed by *Willis* for U_4O_9, and that these can aggregate and extend to larger clusters. In ferrous oxide, neutron scattering from material at high temperatures, in an equilibrium gas buffer atmosphere, has shown that the ratio (cation vacancies)/(tetrahedral cations) agrees with the Koch-Cohen defect complex, with four tetrahedral cations surrounded by thirteen vacant octahedral sites. The same complex is found for all compositions, and over a wide temperature range. These complexes can again cluster to form incipient short range ordering.

In other structures (the rutile and ReO_3 structures and their derivatives), the anion/cation ratio is changed by eliminating a sheet of anion sites along crystallographic shear planes. Regularly recurrent shear planes generate families of homologous compounds; isolated shear planes eliminate large numbers of point defects—oxygen vacancies or interstitial cations—and are already present when the oxygen deficit is extremely small. In reduced rutile of composition $TiO_{1.9986}$ they are already beginning to aggregate into domains of the intermediate phases, and the residual point defect concentration in the rutile structure is less than 10^{-4}. The orientation of the shear planes in the most reduced intermediate phases is different from that in the less reduced phases, or that of isolated extended defects. There is some mechanism for pivoting around

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and, in the Ti—O system, this occurs between $Ti_{10}O_{19}$ and $Ti_{16}O_{31}$, which is the only range of composition in which redox reactions proceed with no hysteresis. In Cr_2O_3—TiO_2, the shear planes pivot gradually from the (121) to the (132) orientation over a wide composition range. In this rotation of shear planes, a crystal can change in composition continuously, without changing the number of shear planes present, but changing their orientation whilst maintaining a nearly constant spacing between them. A phase of this kind has a truly variable composition, whilst remaining fully ordered at every stage. The experimental evidence is that it is energetically advantageous for shear planes to retain their planarity, and bent or curved shear planes have been observed electron microscopically for only a few systems in which true inner equilibrium is attained with difficulty.

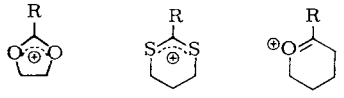
Lecture at Giessen (Germany), May 8, 1973 [VB 371 IE]
German version: Angew. Chem. 85, 833 (1973)

BOOK REVIEWS

Reviews

Abstracts of selected progress reports and review articles

1,3-Dioxolan-2-ylium and related heterocyclic cations are discussed by *C. U. Pittman jr., S. P. McManus,* and *J. W. Larsen.* The authors consider, *inter alia,* 1,3-dioxolan-2-ylium *(1)*, 1,3-dioxan-2-ylium, 1,3-oxathiolan-2-ylium, 1,2-



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

dithiolan-2-ylium, 1,3-dithian-2-ylium *(2)*, 1,3-oxathian-2-ylium, and related cations containing nitrogen, as well as cations of type *(3)*. A survey of recent syntheses is followed by a discussion of the mechanism of the reaction of such cations with bases or nucleophiles. Heterocyclic cations are intermediates in numerous reactions. The ions serve primarily as alkylating agents. [1,3-Dioxolan-2-ylium and Related Heterocyclic Cations. Chem. Rev. *72*, 357—438 (1972); 446 references]

[Rd 619 IE—M]

New free-radical applications in preparative organic chemistry (excluding homolytic arylation of aromatic compounds) are surveyed by *F. Minisci.* The main emphasis is placed on processes whose reactivity and selectivity are controlled primarily by the polar properties of the participating radicals and substrates. Examples: homolytic amination of aromatic compounds, selective alkylation of protonated heteroaromatic bases, Ag-catalyzed oxidative decarboxylation of acids by peroxodisulfate ions, and direct halogenation of alkanes. [Novel Applications of Free-Radical Reactions in Preparative Organic Chemistry. Synthesis *1973*, 1—24; 67 references]

[Rd 620 IE—M]

Topical aspects of electron correlation are reviewed by *P. v. Herigonte.* In nearly all quantum chemical calculations the "independent-particle" model is used for the sake of simplicity. Energies calculated with this model will differ from true energies because interactions between individual particles (correlation) are not accounted for; these differences are termed "correlation energy". In the present review three questions are discussed: 1) To what extent is correlation energy dependent on changes in the geometry of the system? 2) Are there experimental properties which depend directly on electron correlation? 3) Is it really necessary to start with the independent-particle model to get accurate wave functions? There is some evidence that in closed-shell systems correlation energy generally remains invariant during changes in geometry. All that can be said about questions 2) and 3) is that practically nothing is known about the physical meaning of the "independent particle" and hence of correlation. [Electron Correlation in the Seventies. Struct. Bonding *12*, 1—47 (1972); 103 references]

[Rd 633 IE—H]

The properties of the metal-phosphorus bond in coordination compounds are analyzed by *J. G. Verkade* in a detailed discussion of the spectroscopic characteristics of trivalent phosphorus compounds and of their metal complexes. There is also an account of two classes of compounds representing, to a certain extent, phosphorus complexes of coordination number unity: phosphoryl compounds (oxygen atom as acceptor) and adducts with boron compounds. The principal object of this review is to provide the concept of "π back-bonding" with a more quantitative basis. [Spectroscopic Studies of Metal-Phosphorus Bonding in Coordination Complexes. Coord. Chem. Rev. *9*, 1—106 (1972); 308 references]

[Rd 634 IE—H]

The production of refractory transition metal compounds is the topic of a review by *V. N. Gurin.* The significance of the refractory borides, carbides, nitrides, oxides, and silicides of the transition metals is increasing steadily in modern technology. Their production often runs into considerable difficulties, however, because the desired properties are frequently exhibited only by single crystals. The author provides a critical account of, *e.g.*, direct syntheses from the elements, electrolytic processes, metallothermal reductions of metal oxides, and gas phase

processes. [Methods for the Preparation of Refractory Compounds of Transition Metals and Prospects for Their Development. Russ. Chem. Rev. *41*, 323—340 (1972); 377 references]

[Rd 624 IE—Q]

Synthesis, absolute configuration, and optical purity of chiral allenes are considered by *R. Rossi* and *P. Diversi*. The naturally occurring, optically active, chiral allenes include those having the diyne-allene grouping and carotenoids. The asymmetric synthesis of chiral allenes and their resolution by diastereomer formation, as well as the synthesis from a chiral precursor, are illustrated with the aid of several examples. The determination of absolute configuration is also discussed. Determination of the optical purity of chiral allenes is still in its infancy. [Synthesis, Absolute Configuration, and Optical Purity of Chiral Allenes. Synthesis *1973*, 25—36; 83 references]

[Rd 621 IE—M]

Patents

Abstracts of selected "Deutsche Offenlegungsschriften" (DOS), *i. e.* provisionally published specifications as filed with the German Patent Office

A process for the production of transparent rubber-based graft polymers having good impact properties comprises two steps. In the first step, styrene and methyl methacrylate are emulsion-grafted on a rubber latex (especially polybutadiene) in the presence of a free-radical polymerization catalyst to form an intermediate product. In the second step, the grafting reaction is carried further by the addition of more catalyst and monomers in suspension, the emulsion obtained in the first step being converted into a suspension by addition of water and any suspending agent. The graft polymer is obtained in the form of free-running beads, which can be filtered off. [DOS 2155634; Dart Industries Inc., Los Angeles]

[PR 65 IE—Ö]

The preparation of polyethers in the form of fine grains from 1,2-alkylene oxides is achieved in the presence of 0.05 to 10 wt.% of a catalyst based on an alkaline earth metal compound. The catalyst is prepared by reaction, in liquid ammonia, of a) 1 mol of alkaline earth metal hexammine and/or alkaline earth metal amide with b) 0.1 to 1 mole of a 1,2-alkylene oxide and/or a polyepoxide containing 1—5 epoxy groups and c) 0.1—2 mole of a substituted hydrazine *(1)*.

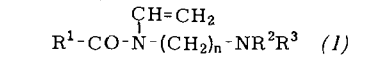
$H_2N\text{-}NR^1R^2$ *(1)*

R^1, R^2 = H, alkyl (C_1 to C_7, possibly substituted with oxygen or nitrogen), cycloalkyl ($C_5 - C_8$), aralkyl ($C_7 - C_{10}$), mononuclear or dinuclear aryl, where R^1 and R^2 may form a heterocycle, possibly together with further atoms.

1,2-Alkylene oxides suitable both for the polymerization and for the preparation of the catalyst include ethylene oxide, propylene oxide, butadienemonoepoxide or butadienediepoxide, ethylene glycol diglycidyl ether, *N,N*-bis-(2,3-epoxypropyl)aniline, and dicyclopentadienediepoxide. The preferred hydrazine compounds are *N*-methylhydrazine and *N,N*-dimethylhydrazine. The properties of the polyethers obtained are good despite the presence of residual catalyst. They are effective flocculating agents and aids for textile treatment and finishing. [DOS 2054664; Badische Anilin- & Soda-Fabrik AG, Ludwigshafen]

[PR 62 IE—Ö]

Modified polyacrylonitrile with basic groups, which exhibits outstanding thermal stability, is prepared by suspension-precipitation copolymerization of acrylonitrile with conventional comonomers in the presence of 0.5 to 5 wt.% (based on the total quantity of monomers) of an amine oxide *(1)* or its salts. Fibers produced from this material have a



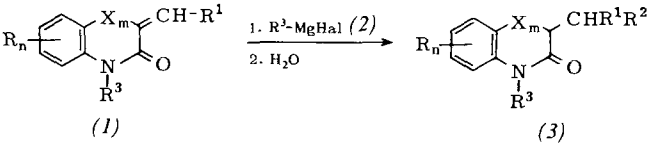
(1)

n = whole numbers from 1—3; R^1 = alkyl, phenyl; R^2, R^3 = alkyl residues, which may be connected to form a ring, possibly with insertion of a heteroatom

good absorptive capacity for acid dyes. [DOS 2049665; Farbwerke Hoechst AG, Frankfurt/Main-Höchst]

[PR 70 IE—T]

Benzoxazine, benzothiazine, and indolinone derivatives *(3)* have a sedative action on the central nervous system and can therefore be used as tranquillizers. The compounds *(3)* also have an antibacterial action, so that they are suitable for use as disinfectants against several types of *Staphylococcus*. To prepare *(3)*, eneketones *(1)* are allowed to react with Grignard compounds *(2)* and the products are



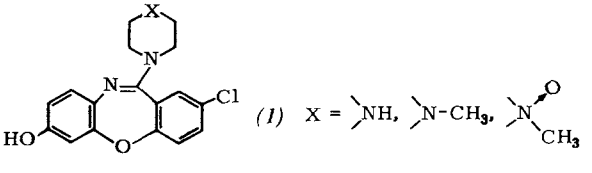
(1) *(3)*

R = halogen, OH, NH_2, NO_2, CF_3, alkyl, alkoxy, alkylthio, dialkylamino; X = O, S, SO, SO_2; R^1 = (substituted) phenyl, naphthyl, thienyl, furyl, pyridyl; R^2 = (substituted) phenyl, cycloalkyl, thienyl, furyl, pyridyl, naphthyl; m = 0, 1; n = 0, 1—4; R^3 = basic residue containing N and bonded *via* lower alkylene.

then hydrolyzed. [DOS 2152282; E.R. Squibb & Sons Inc., New York.]

[PR 94 IE—N]

Chlorohydroxypiperazinyldibenzoxazepines *(1)* and their pharmacologically acceptable salts have one or more of the following effects on the CNS: tranquilizer action, hypnotic and/or muscle-relaxant action, antiemetic action, action against anxiety and depression. They can be prepared from chlorodibenzoxazepinones or from



(1) X = NH, $N\text{-}CH_3$, $N\text{-}CH_3$ (O)

chloropiperazinyldibenzoxazepines by nitration, reduction, and diazotization. [DOS 2153349; American Cyanamid Co., Wayne, N.J.]

[PR 95 IE—N]

Solvent Extraction Reviews. Vol. 1. Edited by *Y. Marcus*. Marcel Dekker, Inc. New York 1971. 1st ed., ix, 256 pp., numerous tables, bound $ 19.50.

The purpose of this review journal is to collect publications on solvent extraction methods which are widely scattered through numerous journals. The reviews, providing relevant information in a more readily accessible way, were to be published at intervals of several months, and then to be annually collected in book form.

The first volume of the series has been published. It contains seven contributions, ranging from fundamental studies to industrial applications: *Z. Kolařik*: Interactions of Acidic Organophosphorus Extractants in the Organic Phase (81 refs.); *C. F. Coleman* and *J. W. Roddy*: Kinetics of Metal Extraction by Organophosphorus Acids (58 refs.); *R. Blumberg*: Industrial Extraction of Phosphoric Acid (41 refs.); *P. Guillaumont* and *C. Miranda*: Solvent Extraction of Protactinium (150 refs.); *W. W. Schultz*: Extraction of Polonium (58 refs.); *J. Y. Oldshue*: Mixing Equipment in Liquid-Liquid Extraction (227 refs.); *A. H. P. Skelland*: Mass Transfer Problems in Liquid Extraction (75 refs.).

The authors make extensive use of standardized abbreviations and definitions as recommended by the editor. This standardization facilitates the reading of solvent extraction papers from various sources. The selection and level of the contributions suggest that "Solvent Extraction Reviews" will be a valuable addition to the proceedings of the International Solvent Extraction Conferences. The reviewer recommends the new series for interested workers in the fields of analytical chemistry, process engineering, radiochemistry, and coordination chemistry.

Werner Müller [NB 140 IE]

Structural Molecular Biology of Phosphates. By *J. Matheja* and *E. T. Degens*. Gustav Fischer Verlag, Stuttgart 1971. 1st ed., xii, 180 pp., 71 figs., DM 88.—.

Research results from two fields of natural science that have hitherto been treated separately are excellently correlated in the present book. The inorganic chemistry of phosphates is treated together with biochemistry, with the result that a bridge that has long been missing has now been formed.

The authors deal first with the inorganic chemistry of phosphates, with particular reference to the theory of structure and coordination, and the results are then applied to biological molecules and molecular complexes in nucleic acids and membranes and to high-energy phosphates and the proton transfer. The chemical evolution of the biological phosphates is then discussed for membranes, phospholipids, and liquid crystals, and ideas on the participation of the phosphates in the primordial phosphate metabolism and in the development of life are presented.

The themes cannot be discussed in full for reasons of space. This is partly compensated for by comprehensive literature references, which make it easy for the interested reader to deepen his knowledge. The present book should not be regarded as a textbook or reference work, but is intended to serve the scientist as a "springboard for continuing research".

For this reason, the book is strongly recommended to everyone working in the field of biochemistry. The reader is confronted with details that he has scarcely encountered before, and he will adopt coordination chemistry as a new argument in his discussions.

W. Saenger [NB 143 IE]

Computer Handling of Chemical Structure Information. By *M. F. Lynch, J. M. Harrison, W. G. Town*, and *J. E. Ash*. Macdonald, London, 1972. 1st ed., xii, 148 pp., 56 figs., bound $ 6.75.

This is an extremely lucid description of a field that has become the center of rapid developments in recent years. Modern chemical documentation, which, according to the author, has changed from a labor-intensive to a capital-intensive activity, is no longer conceivable without computers. Electronic data processing is also being increasingly used as a direct tool of chemical research. The present book fills a need.

The main emphasis is laid on the topological representations (linkage matrices, linear notations) of organic structural formulas and their input, storage, and retrieval. The description is supplemented by typical examples of procedures in practical use and a look ahead at future developments.

Considerable space is devoted to the procedures developed in the Anglo-American countries, particularly those used by the Chemical Abstracts Service. The only methods from outside the English-speaking countries to be discussed are those of the IDC (Frankfurt).

The data compiled in 1968 for a course at the University of Sheffield has been expanded and updated to the position in 1970 (but not the description of the IDC method).

The book is not a manual, since it confines itself to the fundamentals of the methods discussed. However, this material is presented extremely concisely. Literature references are similarly restricted to a few fundamental publications. The authors have been outstandingly successful in presenting the specialist with an objective orientation aid, despite the wealth of publications on this topic. However, those who are less familiar with the field may be misled by the book into an erroneous appraisal of the methods described, since the authors have not only deliberately omitted other important aspects of mechanical documentation in chemistry but also they provide practically no information on the state of development and the limitations of the methods or on their relative importance in present-day practice.

Claus Suhr [NB 146 IE]

Advances in Biochemical Engineering. Vol. 1. Edited by *T. K. Ghose* and *A. Fiechter*. Springer-Verlag, Berlin–Heidelberg–New York, 1971. 1st ed., vii, 194 pp., 70 figs., 25 tables, bound DM 48.—.

The present book is the first volume of a planned series in which numerous authors will report on aspects of modern biotechnology, with emphasis mainly on the mathematical analysis of microbiological systems and vital processes.

The first volume deals with a number of fields that have been neglected until now, such as the dynamics of fermentation liquids, separation of microorganism cells from the culture medium, kinetics of the degradation of cellulose by cellulase, production and use of microbial enzymes, regulation mechanisms in the microorganism cell and their effect on the overproduction of metabolites and enzymes, and the microbial production of biomass from hydrogen and carbon dioxide and from liquid and solid hydrocarbons.

This newly started series, which is unique in its field at present, is extremely welcome as an ambitious and up-to-date reference work for biotechnologists. The chapters in the first volume are clearly arranged, and together with the carefully compiled list of references, they provide a complete survey both of the development of the subject in question and of its present state.

It is to be hoped that this series, which also provides the interested student with a good introduction to biotechnology, will be continued in a similar manner.

Peter Rapp [NB 147 IE]

The Kinetic Isotope Method and its Application. By *M. B. Neiman* and *D. Gál*. Elsevier Publishing Company, Amsterdam–London–New York 1971. 1st ed., xii, 309 pp., numerous figures and tables, bound $ 26.50.

The central theme of this book is the kinetic isotope method developed by *Neiman* for the investigation of chemical reactions, and later successfully used by *Gál*.

The theoretical principles are described in the first three chapters, and practical examples are discussed in detail in Chapters 4–10. Very many data from original publications are used for this purpose.

As early as Chapter 1, the reader is confronted with a very complicated example of the use of the kinetic isotope method. This example does not seem particularly suitable for demonstrating the use of the method, particularly since many assumptions are made. Chapters 2 and 3 present a very formal but nevertheless very consistent account of the method. From page 36 (Chapters 4 *et seq.*), particular examples are discussed in detail: reactions in open systems (Chapter 4), thermal decomposition reactions (Chapter 5), oxidation of hydrocarbons in the gas phase (Chapter 6), free-radical reactions (Chapter 7), oxidation reactions in the liquid phase (Chapter 8), heterogeneous catalysis (Chapter 9), applications in biochemistry (Chapter 10). The book will undoubtedly be a very useful acquisition for the specialist who is interested in the practical examples provided. It seems less suitable for scientists or students approaching this field for the first time.

K. H. Lieser [NB 149 IE]

Recent Books

The following books have been received by the editor. Detailed reviews will not be published in all cases because of the limited space available under this heading in the journal.

Advances in Catalysis, Vol. 23. Edited by *D. D. Eley, H. Pines*, and *P. B. Weisz*. Academic Press, New York—London 1973. x, 352 pp., bound $ 19.00.

Contents: Metal Catalyzed Skeletal Reactions of Hydrocarbons; Specificity in Catalytic Hydrogenolysis by Metals; The Chemisorption of Benzene; The Electronic Theory of Photocatalytic Reactions on Semiconductors; Cycloamyloses as Catalysts; Pi and Sigma Transition Metal Carbon Compounds as Catalysts for the Polymerization of Vinyl Monomers and Olefins.

Radiation Chemistry of Macromolecules, Vol. 2. By *M. Dole*. Academic Press, New York, London 1973. xvii, 406 pp., bound $ 25.00.

Contents: Radiation Chemistry of Substituted Vinyl Polymers; Radiation Chemistry of Some Miscellaneous Polymers; The Effect of Radiation on Oxidation, Mechanical Properties, and Physical State; Macromolecules of Biological Interest.

Synergetics. Cooperative Phenomena in Multi-Component Systems. Edited by *H. Haken*. B. G. Teubner, Stuttgart 1973. 279 pp., stitched DM 54.—.—Proceedings of the Symposium on Synergetics, April 30 to May 6, 1972, Schloss Elmau.

Photochemistry IV. Edited by International Union of Pure and Applied Chemistry, Division of Organic Chemistry. Butterworths, London 1973. vi, 410 pp., bound £ 6.80.—Plenary Lectures from the 4th International Symposium on Photochemistry, July 16—22, 1972, Baden-Baden.

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α-Peroxyamines

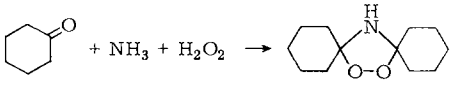
By E. G. E. Hawkins[*]

α-Peroxyamines contain the group $>N-\underset{|}{\overset{|}{C}}-O-O-$, which may also be incorporated into a ring. Numerous compounds of this type are accessible, *inter alia*, from ketones, hydrogen peroxide, or alkyl hydroperoxides and ammonia, as well as by autoxidation or photo-oxidation of amines or imines. Apart from decomposition reactions, the chemistry of these compounds is characterized by interesting cyclizations to give lactams, imides, oxaziridines, tetroxanes, *etc.*

1. Introduction

Although isolated examples of α-peroxyamines have been described in the literature, either as definite compounds or as possible intermediates in oxidation reactions, over a number of years, a systematic study of these substances (including novel cyclic 1,2,4-dioxazolidines) has been pursued only recently.

Our work in this field originated from the discovery of the new compound 3,3';5,5-bis(pentamethylene)-1,2,4-dioxazolidine *(1)* during a study of the reaction of cyclohexanone, ammonia, and hydrogen peroxide, in the presence of tungstate catalysts, reported to give cyclohexanone oxime (for references see[4]), and its decomposition to caprolactam (with bases) and 11-cyanoundecanoic acid (on pyrolysis)—which on hydrogenation provided 12-aminododecanoic acid, the monomer of Nylon 12. Extension of this work to the related peroxyamines was a natural sequel.



(1)

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Great Burgh
Yew Tree Bottom Road
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This review is intended to describe the preparation and reactions of α-peroxyamines where the peroxy group is α to nitrogen, but does not include α-peroxyhydrazines nor α-peroxyazo compounds, and omits references to oxygenation reactions where α-peroxyamines are probable intermediates but where their isolation has not been possible.

2. *N*-Unsubstituted α-Hydroperoxyamines [$R^1R^2C(OOH)NH_2$]

2.1. Formation

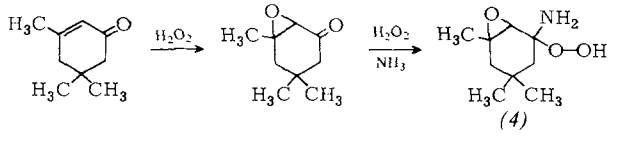
Early work with these compounds is sparse. *Schenck*[1] has stated, without detail, that they are formed by photooxidation of amines, but their isolation would have been difficult in view of the ease with which they undergo decomposition and further reaction under the experimental conditions. Small amounts of α-hydroperoxycyclohexylamine *(2)* were isolated during photo-oxidation of cyclohexylamine[2], but the major products were the amine-hydrogen peroxide adduct, and imines and amides, all of which are probably produced *via* the α-hydroperoxyamine.

The presence of *(2)* was detected, by thin-layer chromatography, in the products of ozonolysis of bis(cyclohexylidene) in the presence of ammonia[3], but was identified

only by means of the *N*-benzoyl derivative of its dehydration product, 2-pentamethyleneoxaziridine *(3)*.

(2) *(3)*

However, α-hydroperoxycyclohexylamine *(2)* may be prepared as a solid in high yield by direct reaction of cyclohexanone, hydrogen peroxide (molar ratio *ca.* 1:1), and ammonia[4]. It is unstable at room temperature, particularly when impure, and easily reverts to cyclohexanone, with loss of ammonia; storage for several weeks at −20 °C is possible. The corresponding α-hydroperoxyamines were similarly obtained, in varying yields, from other cyclic

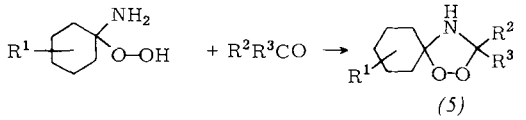


(4)

ketones (3- and 4-methylcyclohexanone, cycloheptanone, cyclododecanone, and dihydroisophorone)[5], but none was isolated from acyclic carbonyl compounds[6]. The β,γ-unsaturated ketone isophorone yielded the β,γ-epoxy-4-hydroperoxyamine *(4)* *via* the epoxide.

2.2. Reactions

The α-hydroperoxyamines reacted with carbonyl compounds to give moderate yields of 1,2,4-dioxazolidines—cyclic peroxyamines—*(5)*[4,5]. However, the products frequently also contained symmetrical cyclic peroxyamines through reaction of hydrogen peroxide and ammonia, produced by breakdown of the hydroperoxyamine, with the more reactive of the carbonyl compounds present.



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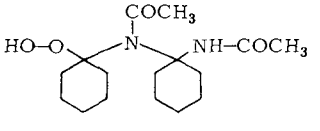


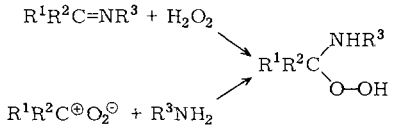
(6)

α-Hydroperoxycyclohexylamine *(2)* reacted with: (i) ferrous sulfate to yield cyclohexanone with some hexanamide and hexanoic acid; (ii) ferrous chloride to give cyclohexanone, ω-chlorohexanamide, and ω-chlorohexanoic acid; and (iii) sodium tungstate or tungstophosphoric acid to provide cyclohexanone oxime. Pyrolysis of *(2)* at 450 to 500 °C/150 torr gave products similar to those derived from 3,3;5,5-bis(pentamethylene)-1,2,4-dioxazolidine *(1)* (Section 8.1), whilst attempts at acetylation yielded a solid peroxide, thought to have the structure *(6)*, which decomposed to cyclohexanone and acetamide at higher temperatures.

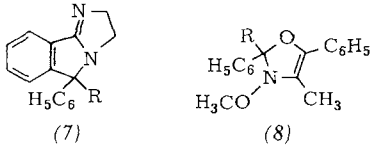
3. *N*-Monosubstituted α-Hydroperoxyamines [$R^1R^2C(OOH)NHR^3$]

3.1. Formation

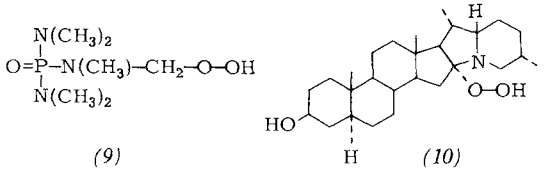
Compounds of this class have been obtained by reaction of imines with ethereal[7] or aqueous[8] hydrogen peroxide or by ozonolysis of olefins in the presence of a primary amine[3].



Hydroperoxides have been isolated from oxygenation products of certain cyclic amines, *e.g. (7)*, R = O—OH, from *(7)*, R = H[9], and *(8)*, R = O—OH from *(8)*, R = H[10], whilst photo-oxidation of hexamethylphosphoramide gave rise to the unstable *(9)*[11] which decomposed to give formaldehyde or formic acid.

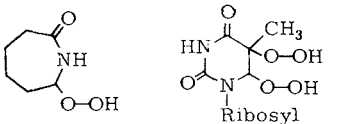


(7) *(8)*

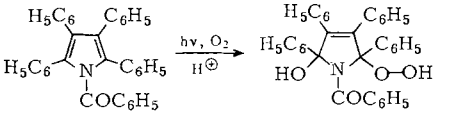


(9) *(10)*

Oxidation of 3β-hydroxysolanide-16(N)-eninium perchlorate with alkaline hydrogen peroxide provided the α-hydroperoxyamine *(10)*, which could be reconverted to the starting compound by dilute perchloric acid in methanol[12].

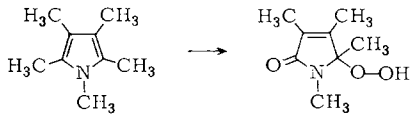


(11) *(14)*

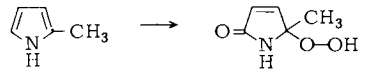


(12) *(13)*

A number of α-hydroperoxyamides have been produced, either by autoxidation [*e.g. (11)* from caprolactam[13]], photooxidation [*e.g. (13)* from *(12)*[14]], irradiation [*e.g. (14)* from thymidine[15]], or reaction of hydrogen peroxide with enamines [*e.g. (16)* from *(15)*[16]; *(18)* from *(17)*[17]; *(20)* from *(19)*, R = H, CH_3[18]; and *(22)* from *(21)*, R = CH_3, $C_6H_5CH_2$[19]].



(15) (16)



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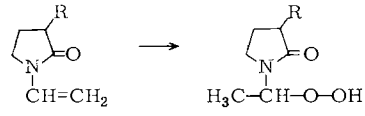

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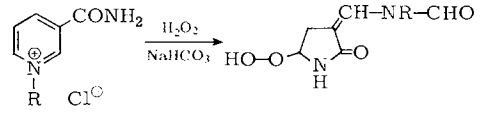
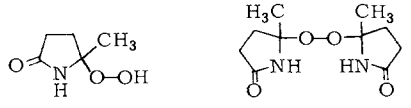


(21) (22)

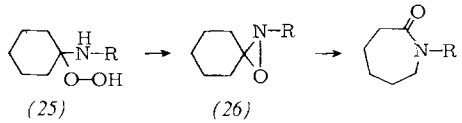
Reaction of hydrogen peroxide and ammonia with ethyl levulinate or levulinamide yielded both the hydroperoxylactam *(23)* and peroxydilactam *(24)*[6].



(23) (24)

3.2. Reactions

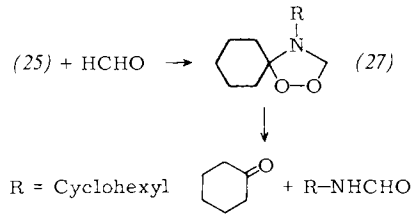
Many α-hydroperoxyamines, when heated in a solvent[7, 3] or treated with acids[8] (*e.g.* acetic acid/acetic anhydride), are converted into the corresponding oxaziridine; *N*-cyclohexyl-1-hydroperoxycyclohexylamine *(25)* is converted into *N*-cyclohexylcaprolactam (and *N*-cyclohexylidenecyclohexylamine) by lithium chloride in methanol, presumably *via* the oxaziridine *(26)*[8].



(25) (26)

R = Cyclohexyl

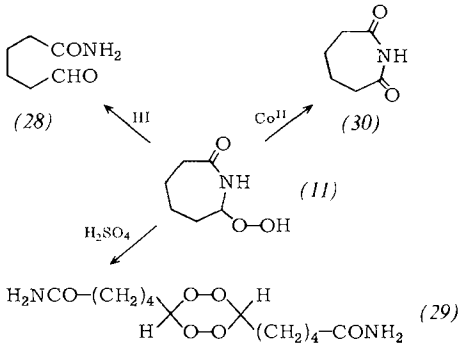
With alkali *(25)* gives the corresponding imine by loss of hydrogen peroxide, and with acidified ferrous sulfate it is partly converted into *N*-cyclohexylhexanamide and *N,N'*-dicyclohexyldodecanamide[8], products similar to those from treatment of the corresponding oxaziridine *(26)* with ferrous sulfate[20]. Reaction of *(25)* with formaldehyde gives the unstable 1,2,4-dioxazolidine *(27)*, which decomposes on storage at room temperature to form cyclohexanone and *N*-cyclohexylformamide[8].



(25) + HCHO → *(27)*

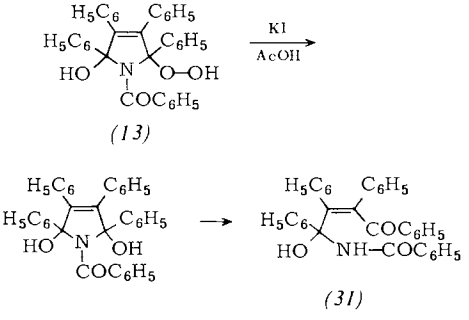
R = Cyclohexyl + R–NHCHO

The α-hydroperoxylactam *(11)* was reduced by hydriodic acid to the ω-formyl amide *(28)*[13], and converted into a 1,2,4,5-tetroxane *(29)* by 70—80% sulfuric acid[21] and into adipimide *(30)* by cobalt-catalyzed decomposition[13].



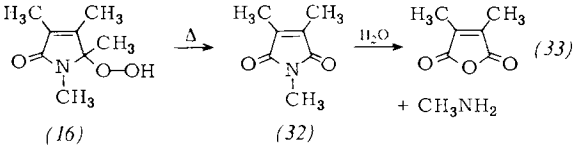
(28) *(30)* *(11)* *(29)*

Hydroperoxide *(13)* is reduced by potassium iodide/acetic acid to the corresponding diol which, in polar solvents, undergoes ring opening to yield *(31)*[14].



(13) *(31)*

Thermal decomposition of *(16)* led to the imide *(32)* by loss of methanol, and further treatment with water gave an anhydride *(33)* and methylamine[16].



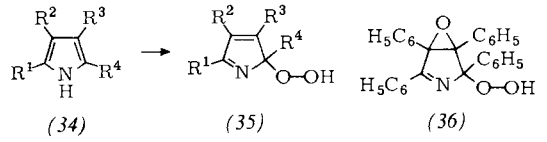
(16) *(32)* *(33)* + CH_3NH_2

4. *N*-Substituted α-Hydroperoxyimines [$R^1R^2C(OOH)N{=}R^3$]

4.1. Formation

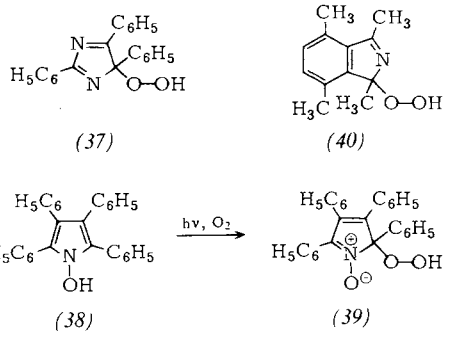
Photosensitized oxygenation of certain substituted pyrroles *(34)* [(*a*) $R^1{=}R^2{=}R^3{=}R^4{=}C_6H_5$[22]; (*b*) $R^1{=}R^4{=}$

C_6H_5, $R^2=R^3=H$; (*c*) $R^1=R^2=R^4=(CH_3)_3C$, $R^3=H$; (*d*) $R^1=R^4=(CH_3)_3C$, $R^2=R^3=H$[23]] has produced the corresponding 2-hydroperoxy-2*H*-pyrroles *(35)*; the tetraphenyl compound *(35a)*, together with the epoxyhydroperoxide *(36)* and a number of other products, was



(34) *(35)* *(36)*

also obtained by treatment of tetraphenylpyrrole *(34a)* with hydrogen peroxide[24]. Similar photo-oxidation of 2,4,5-triphenylimidazole (lophine)[25,26], or reaction of dilute hydrogen peroxide with the 2,4,5-triphenylimidazyl radical[25], gave rise to a related α-hydroperoxyimine *(37)*, and photo-oxidation of 1-hydroxytetraphenylpyrrole *(38)* provided an α-hydroperoxynitrone *(39)*[27]. Autoxi-

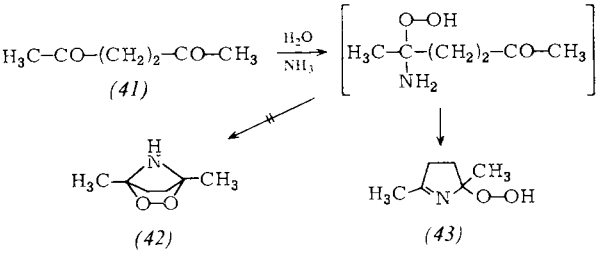


(37) *(40)*

(38) *(39)*

dation of 1,3,4,7-tetramethylisoindole in benzene/ether at room temperature led to the formation of the hydroperoxide *(40)*[28].

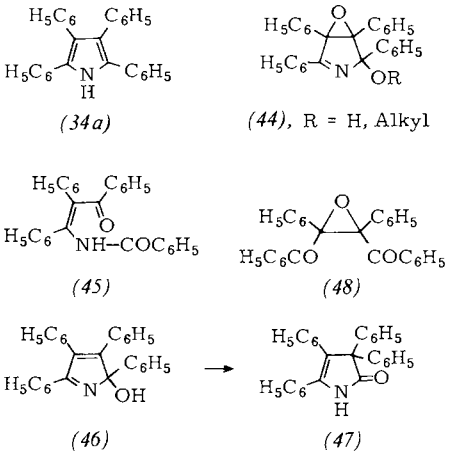
The anticipated formation of a bicyclic peroxyamine *(42)* from the reaction of 2,5-hexanedione *(41)* with hydrogen peroxide and ammonia did not occur; instead, the hydroperoxypyrroline *(43)* was obtained and intramolecular cyclization may have been prevented by steric hindrance[6].



(41) *(42)* *(43)*

4.2. Reactions

The reactions of 2-hydroperoxytetraphenyl-2*H*-pyrrole *(35a)* ($R^1=R^2=R^3=R^4=C_6H_5$) have been studied in depth[22,24,28]. Thermal decomposition of neat *(35a)* brings about formation of tetraphenylpyrrole *(34a)* and liberation of oxygen. A similar reaction occurs when heating is carried out in nonpolar solvents, but in polar solvents (*e.g.* alcohols) the major products are 5-hydroxy(or 5-alkoxy)-3,4-epoxytetraphenylpyrroline *(44)* and the amide *(45)*.



(34a) *(44)*, R = H, Alkyl

(45) *(48)*

(46) *(47)*

Strong acids convert *(35a)* into hydrogen peroxide and a salt of the corresponding hydroxy compound *(46)*, whereas strong bases afford the lactam *(47)*, which is also formed by rearrangement of *(46)* on heating. Treatment of *(35a)* with hydrogen peroxide in neutral solvents (dioxane or ethanol) yields largely the epoxide *(36)*, but in acetic acid ring-opening occurs with production of *(45)* and *(48)*.

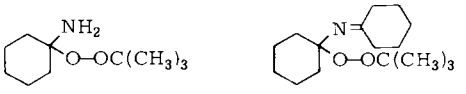
Similar products to *(48)*, on storage, and *(46)* and *(47)*, on reduction with potassium iodide/acetic acid, have been obtained from the 2-hydroperoxy-2,5-di-*tert*-butyl- and 2,4,5-tri-*tert*-butyl-2*H*-pyrroles *(35d)* and *(35c)* respectively[23].

The hydroperoxypyrroline *(43)* was converted into 2,5-dimethylpyrrole by sodium methoxide, 2,5-hexanedione by ferrous sulfate, and a mixture containing these two compounds on pyrolysis[6].

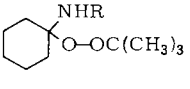
5. *N*-Unsubstituted α-Alkylperoxyamines [$R^1R^2C(OOR^3)NH_2$]

5.1. Formation

Treatment of cyclohexanone with ammonia and *tert*-butyl hydroperoxide gave an equilibrium mixture which contained 1-*tert*-butylperoxycyclohexylamine *(49)*; distillation of the product led to some decomposition, with loss of *tert*-butyl hydroperoxide. Spectroscopic examination of the higher-boiling reaction products suggested that the peroxyimine *(50)* was also formed by further reaction of *(49)* with cyclohexanone. The 1-*tert*-butylperoxycyclohexylamine *(49)* provided normal amine derivatives *(51)*



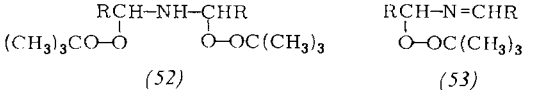
(49) *(50)*



(51), R = $CONHC_6H_5$, CH_3CO, C_6H_5CO, $CO_2C_2H_5$, Tosyl, Cl

with phenyl isocyanate, acetyl chloride, benzoyl chloride, ethyl chloroformate, *p*-toluenesulfonyl chloride, and *tert*-butyl hypochlorite[29].

Replacement of *tert*-butyl hydroperoxide by cumene hydroperoxide gave a crude product containing the peroxycyclohexylamine corresponding to *(49)*, but although this could not be distilled without decomposition its presence was proved by formation of a crystalline phenylurea derivative.

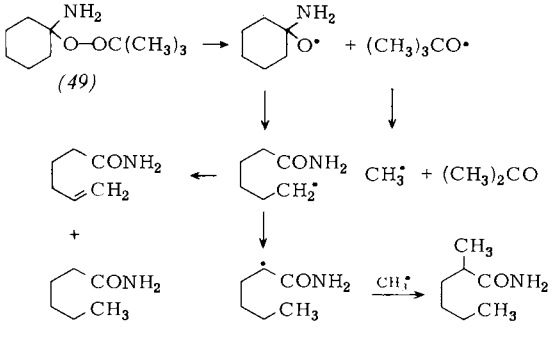


(52) *(53)*

No similar α-alkylperoxyamines could be isolated when starting with acyclic ketones (2-butanone and 3-pentanone), and acyclic aldehydes (acetaldehyde and *n*-butyraldehyde) gave products thought to be largely the diperoxyamines *(52)*, which on distillation tended to lose a molecule of *tert*-butyl hydroperoxide with formation of imines *(53)*[29].

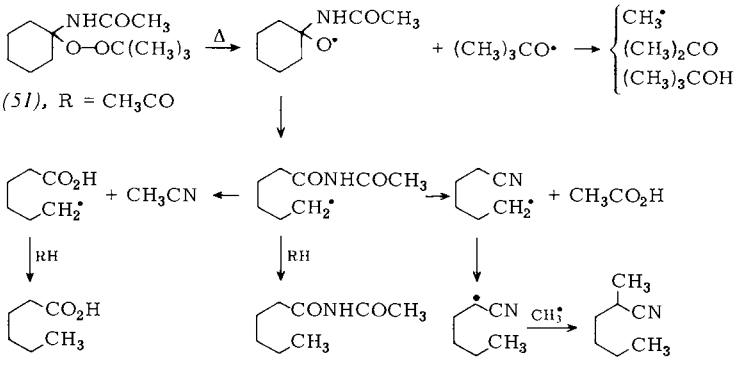
5.2. Reactions

Decomposition of *(49)* by sodium methoxide led to evolution of ammonia and formation of cyclohexanone, whereas pyrolysis at 450—550 °C gave cyclohexanone, acetone, unsaturated and saturated C_6 amides, a C_7 branched amide and traces of nitriles and acids. This thermal decomposition evidently involves both reconversion to cyclohexanone and *tert*-butyl hydroperoxide and homolytic scission of the O—O bond, followed by ring opening and methylation of 1,5-rearranged radicals:



(49)

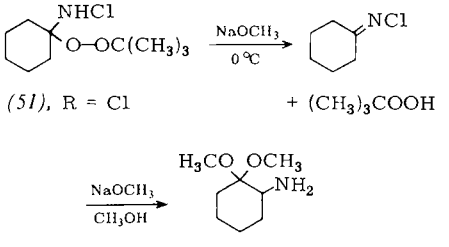
Pyrolysis of the *N*-acetyl derivative *(51)*, R = CH_3CO, led to a complex mixture of products including acetone, *tert*-butanol, cyclohexanone, acetic acid, hexanoic acid, acetamide, α-methylhexanenitrile (reported[29] incorrectly as α-methylpentanenitrile) and *N*-acetylhexanamide, as well as smaller amounts of lower molecular weight compounds. The main products are formed in free-radical reactions.



(51), R = CH_3CO

Reaction of the *N*-acetyl derivative with sodium methoxide proceeded *via* *N*-1-cyclohexenylacetamide to cyclohexanone and acetamide.

N-Chloro-*tert*-butylperoxycyclohexylamine *(51)*, R = Cl, also lost *tert*-butyl hydroperoxide on treatment with sodium methoxide to give *N*-chlorocyclohexylideneimine and thence, by a Neber reaction, 2,2-dimethoxycyclohexylamine.

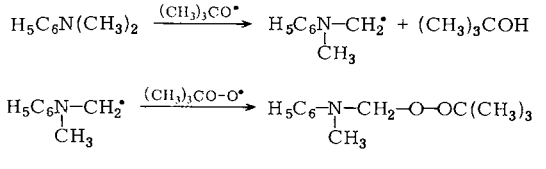


(51), R = Cl

6. *N*,*N*-Disubstituted α-Alkylperoxyamines [$R^1R^2C(OOR^3)NR^4R^5$]

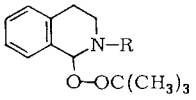
6.1. Formation

When *tert*-butyl hydroperoxide was heated with dimethylaniline in the presence of heavy metal ions *N*-*tert*-butylperoxymethyl-*N*-methylaniline was produced in high yield[30].



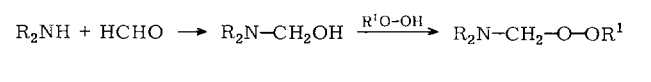
A number of 1-*tert*-butylperoxy-2-aryl-1,2,3,4-tetrahydroisoquinolines *(54)* have been similarly prepared by treat-

ment of the corresponding 2-aryltetrahydroisoquinoline with *tert*-butyl hydroperoxide and cuprous chloride in benzene[31].

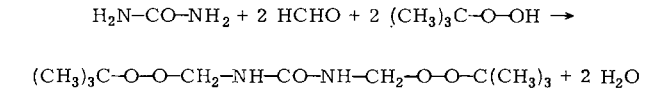


(54)

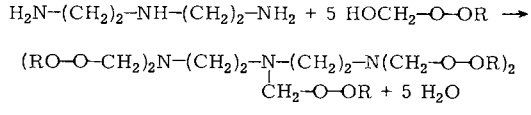
N,N-Disubstituted α-peroxyamines have also been synthesized in good yields by treatment of a secondary amine with formaldehyde and a hydroperoxide[32] or hydrogen peroxide[33].



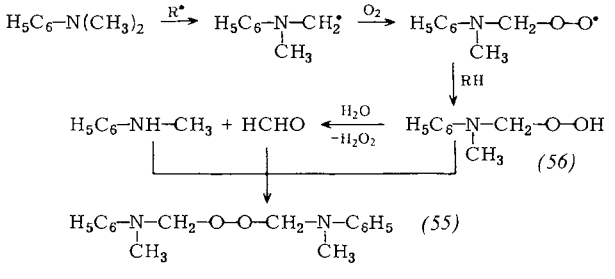
The mixture of amine and formaldehyde may be replaced by the preformed *N*-hydroxymethylamine, and the less reactive amides undergo a similar reaction in the presence of acids[32].



Similarly, α-hydroxymethyl peroxides and primary or secondary amines yield α-peroxyamines[34].

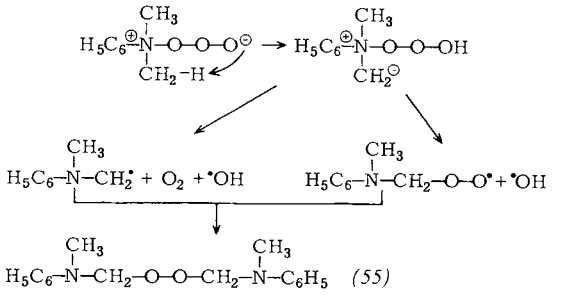


A number of symmetrical peroxyamines of type *(55)* were also produced by autoxidation of tertiary aromatic amines in the presence of an initiator[33,35], and it was suggested that the nonisolated α-hydroperoxyamines, *e.g. (56)*, were intermediates.

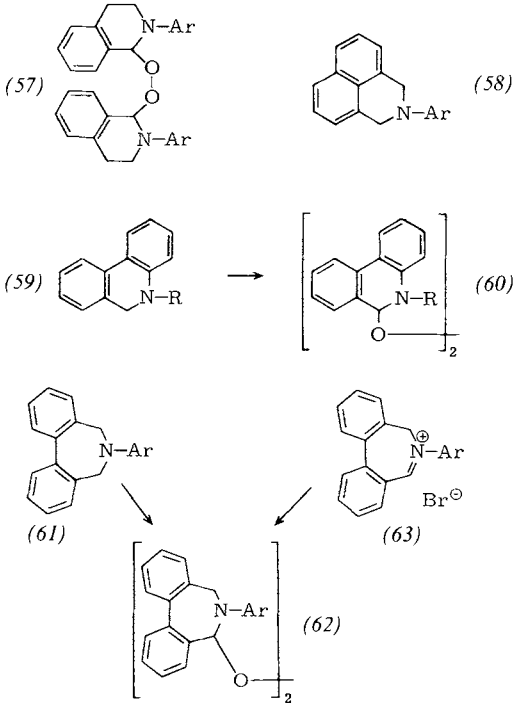


Similar symmetrical compounds have been obtained by ozonization of tertiary aromatic amines at low temperatures in nonpolar solvents, with a suggested mechanism involving initial attachment of the ozone to the nitrogen atom[36].

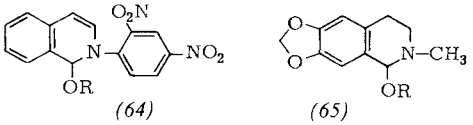
It was found that benzene solutions of *N*-aryl-substituted tetrahydroisoquinolines, on shaking with oxygen in UV light, were converted into the corresponding crystalline



bis(*N*-aryltetrahydro-1-isoquinolyl) peroxides *(57)*[37], whereas the *N*-alkyl- and 1,2-disubstituted compounds did not autoxidize[38]. Of the tricyclic amines examined, the *N*-substituted 2,3-dihydro-1*H*-benz[*d,e*]isoquinolines *(58)* did not react under similar conditions, whereas both *N*-substituted 5,6-dihydrophenanthridines *(59)*[38] and *N*-aryl-6,7-dihydro-5*H*-dibenz[*c,e*]azepines *(61)*[39] gave the symmetrical peroxides *(60)* and *(62)* respectively.

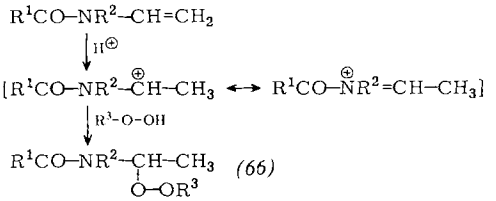


Higher yields of these symmetrical peroxyamines, *(57)* and *(62)*, were obtained by reaction of hydrogen peroxide with the corresponding dihydroisoquinolinium (or azepinium) bromide *(63)*. A similar type of reaction, with *N*-methyl-6,8-dinitroquinolinium chloride, had previously been used for obtaining crystalline derivatives from a number of primary, secondary, and tertiary hydroperoxides[40], whilst pseudo-bases [*e.g. (64)* and *(65)*, where R = H] may also be converted into peroxides [*(64)* and *(65)*, where R = OR^1] by treatment with hydroperoxides (R^1OOH)[40].

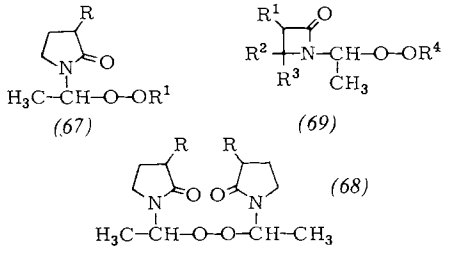


(64) (65)

A related synthesis of α-peroxy-*N*-acyl (or *N*-sulfonyl) amines, *e.g. (66)*, involves the reaction of *N*-acyl- (or *N*-sulfonyl-)*N*-vinylamines with tertiary alkyl hydroperoxides or hydrogen peroxide in the presence of acid catalysts (SO_2Cl_2 or $SOCl_2$) at low temperatures[18,41]; *N*-vinyllactams give the peroxides *(67)*, *(68)*, and *(69)*.

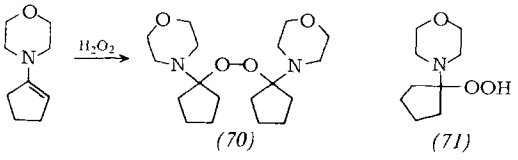


(66)



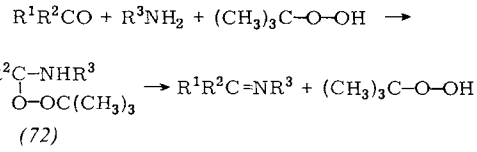
(67) *(69)* *(68)*

The enamines derived from cyclic ketones and cyclic secondary amines (morpholine or piperidine) react with ethereal hydrogen peroxide to give symmetrical α,α'-diamino peroxides[42], *e.g. (70)*, although use of more hydrogen peroxide gives rise to the intermediate α-hydroperoxyamine *(71)*[43].



(70) *(71)*

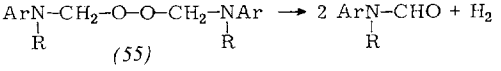
The reaction of cyclic ketones or acyclic aldehydes (but not acyclic ketones) with primary amines and *tert*-butyl hydroperoxide also yielded α-peroxyamines *(72)*; the lower-molecular-weight products were stable to distillation but the higher-boiling homologs decomposed into the corresponding imines[8].



(72)

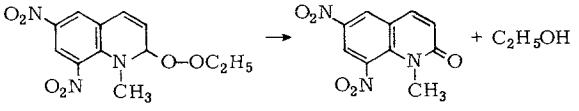
6.2. Reactions

The symmetrical peroxides of type *(55)* were easily converted back into secondary amine, formaldehyde, and hydrogen peroxide by acids[33], but, surprisingly for diprimary peroxides, are reported to be stable to alkali. They may be hydrogenated to the corresponding dialkylanilines, and on thermal decomposition in toluene yield an *N*-alkylformanilide and hydrogen (comparable with the production of formic acid and hydrogen on heating bis(hydroxymethyl) peroxide[44]).

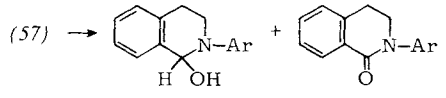


(55)

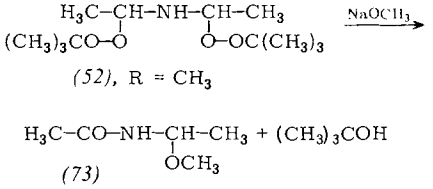
Base-catalyzed decomposition of the peroxides derived from primary or secondary hydroperoxides and *N*-methyl-6,8-dinitroquinolinium chloride (*e.g.* in pyridine) proceeds by the normal Kornblum-De La Mare mechanism[45] to give the corresponding quinolone[40]:



Peroxides *(57)* and *(60)*, when heated, disproportionated into pseudo-bases and lactams[37,38].



Pyrolysis of the α-*tert*-butylperoxyamines *(72)*, as well as their reaction with sodium methoxide, gave mainly the corresponding imine (by loss of *tert*-butyl hydroperoxide), although the thermal decomposition of *N*-ethyl-1-*tert*-butylperoxycyclohexylamine provided a product containing *N*-ethylamides indicative of homolytic fission of the peroxide bond[8].



(52), R = CH_3

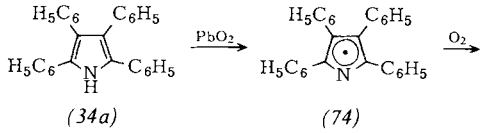
(73)

Reaction of the diperoxyamine *(52)*, R = CH_3, with sodium methoxide gave mainly the α-methoxyamide *(73)*, as well as acetamide; evidently, Kornblum-De La Mare reaction occurred at one of the peroxide systems whereas in the second simple replacement of the *tert*-butylperoxy group by methoxyl took place[29].

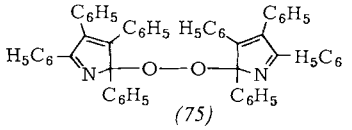
7. *N*-Substituted α-Alkylperoxyimines [$R^1R^2C(OOR^3)N{=}R^4$]

Autoxidation of the radical *(74)*, produced by reaction of 2,3,4,5-tetraphenylpyrrole *(34a)* with lead dioxide, led to the formation of the peroxide *(75)*, easily reduced to the hydroxypyrrole *(46)* by hydriodic acid[28].

The same peroxide *(75)* was obtained (in 20% yield) during electrochemical oxidation of tetraphenylpyrrole in the presence of sodium carbonate and air[46].

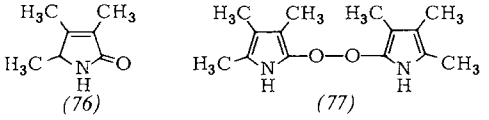


(34a) (74)

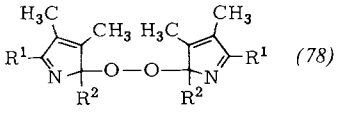


(75)

Oxidation of 2,3,4-trimethylpyrrole by hydrogen peroxide in pyridine gave mainly the lactam *(76)*, but a by-product peroxide (previously described[47]) was assigned the structure *(77)*[48]; however, it seems more likely that this peroxide was *(78)* with either $R^1=CH_3$, $R^2=H$ or $R^1=H$, $R^2=CH_3$.



(76) (77)



(78)

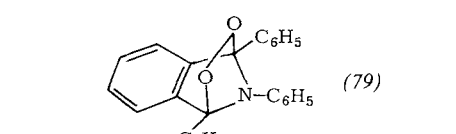
Reaction of the 2,4,5-triphenylimidazyl radical with a tertiary hydroperoxide (*tert*-butyl or cumyl) gave the corresponding 4-peroxyimidazole[25], and related chemiluminescent peroxides were obtained with phenyl replaced by other aryl groups[49].

8. 1,2,4-Dioxazolidines

8.1. Formation

Earlier work on the production of these cyclic peroxyamines appears to have been limited to the photo-oxidation of 1,2,3-triphenylisoindole, leading to high yields of the compound *(79)*[50].

Recently it has been found that aldehydes and ketones (both acyclic and cyclic), when treated with ammonia and hydrogen peroxide, give rise to symmetrical cyclic peroxyamines (1,2,4-dioxazolidines) *(80)*[4-6]. The carbonyl compounds used included acetaldehyde, *n*-butyraldehyde, acetone, 2-butanone, cyclohexanone, cyclopentanone, cycloheptanone, 2-, 3-, and 4-methylcyclohexanone, isophorone, and dihydroisophorone, and the peroxyamines formed, sometimes solid, could all be distilled without decomposition under reduced pressure. In those cases where the intermediate α-hydroperoxyamine (Section 2.1) could be isolated, further reaction with the ketone gave the cyclic compounds *(80)*, also formed from the corresponding bis(1-hydroxyalkyl) peroxides and ammonia, *e.g.* *(1)* from *(81)*.



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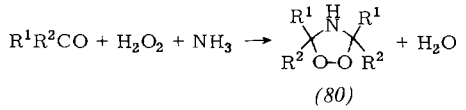

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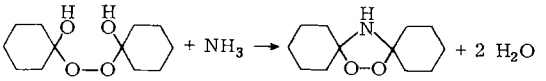
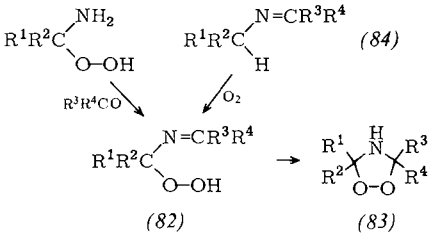


(81) (1)

Unsymmetrical 1,2,4-dioxazolidines *(83)* [see also *(5)*] could be obtained from α-hydroperoxyamines and a different carbonyl compound, although yields were often poor and the product contaminated with one or both of the symmetrical dioxazolidines. Presumably reaction proceeded *via* cyclization of the α-hydroperoxyimine, and the possibility of the formation of such intermediates by autoxidation (or photo-oxidation) of the corresponding imine *(84)* can be envisaged.



(84) (82) (83)

However, in general, attack of oxygen occurs at the methylene (or methine) group α to carbon of the C=N system[51]. Exceptions to this generalization are imines having the methylene (or methine) group α to nitrogen activated, *e.g.*, by aryl groups (cf. Section 4.1); thus, when R^1 = aryl and R^2 = alkyl or aryl, autoxidation (or photo-oxidation) at low temperatures (0 to −20 °C) led to the production of 1,2,4-dioxazolidines *(83)*, R^3, $R^4=-(CH_2)_5-$, in good yield[51]. Oxygenation of the imine *(84)*, $R^1=R^2=R^3=R^4=C_6H_5$, was extremely slow, and under forcing conditions the products obtained (benzophenone and benzanilide) were those expected from decomposition of the corresponding peroxyamine.

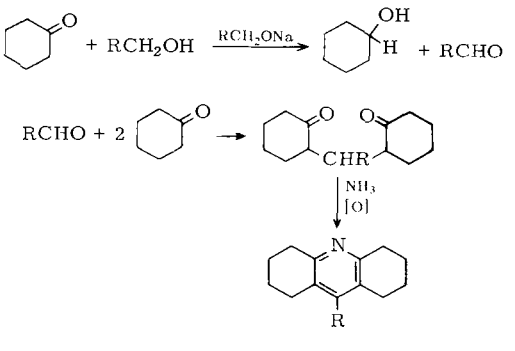
8.2. Reactions

The most detailed reaction study was carried out with 3,3;5,5-bis(pentamethylene)-1,2,4-dioxazolidine *(1)*, but the behavior of the other members of this class of compounds is very similar.

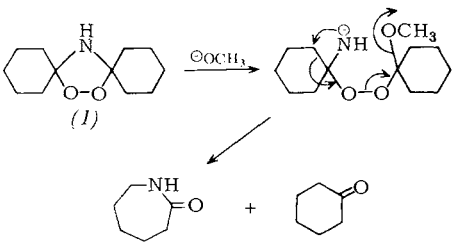
The amine group may be acetylated (by acetyl chloride) chlorinated (by *tert*-butyl hypochlorite), methylated (by methyl iodide/silver carbonate), or converted into a phenylurea (by phenyl isocyanate). Catalytic hydrogenation of *(1)* leads to cyclohexylamine or cyclohexanone, whereas treatment with aqueous acids or bases gives cyclohexanone.

With formic acid or acetic acid the cyclohexanone is accompanied by some caprolactone (through Baeyer-Villiger reaction) and ammonium formate or acetate. Treatment of *(1)* with warm ferrous sulfate afforded low yields of hexanamide and dodecanediamide, whereas ferrous chloride and cuprous chloride gave ω-chlorohexanamide and heating with copper naphthenate (catalytic amount) led to 5-hexenamide[4].

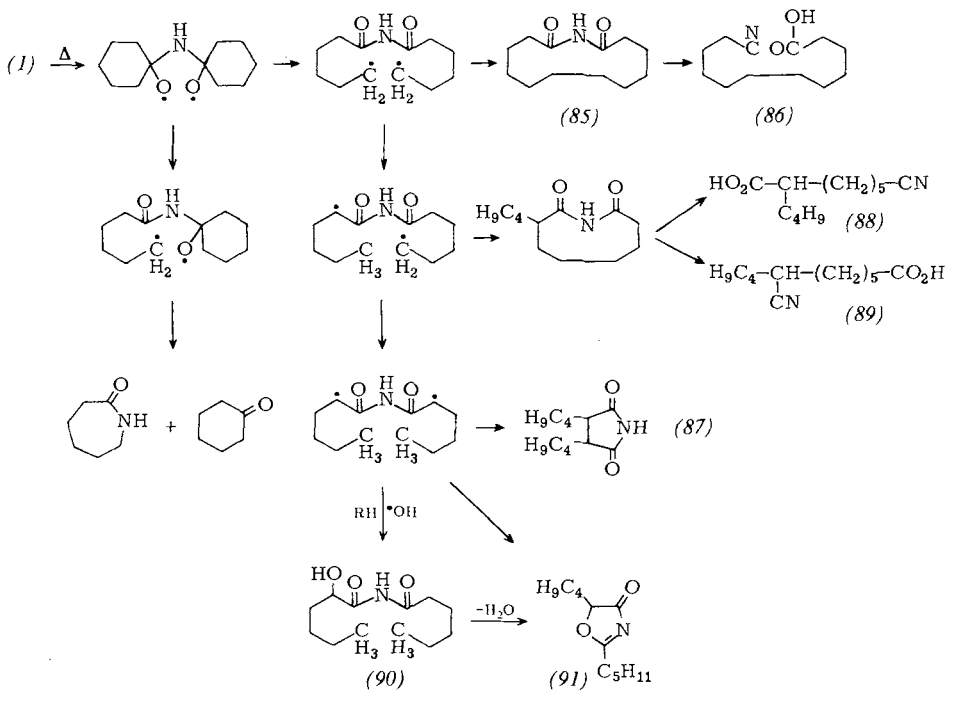
The reactions of *(1)* which were of the greatest interest were its decomposition by certain bases and its pyrolysis. When heated in methanolic solution with sodium methoxide or phenoxide, an alkali-metal hydroxide, or lithium chloride or bromide, the peroxyamine was converted in high yield into caprolactam and cyclohexanone. The use of other alkoxides, sodamide in benzene, or organic bases (*e. g.* amines) gave variable and often low yields of caprolactam, and the by-products included 2-(1-cyclohexenyl)cyclohexanone, hexanamide, 5-hexenamide, and octahydroacridines. Formation of 9-alkyl-1,2,3,4,5,6,7,8-octahydroacridines increased when higher alkoxide/alkanol systems were used, and they were then accompanied by cyclohexanol; presumably the greater activity of such alkoxides as catalysts in bringing about Oppenauer-Ponndorf oxidation-reduction reactions leads to such products.



The mechanism of formation of caprolactam and cyclohexanone probably involves nucleophilic attack of the methoxy-ion at the spiro-carbon site; removal of hydrogen from the imino group is not involved since *N*-methyl-1,2,4-dioxazolidine, under similar conditions, yields cyclohexanone and *N*-methylcaprolactam.

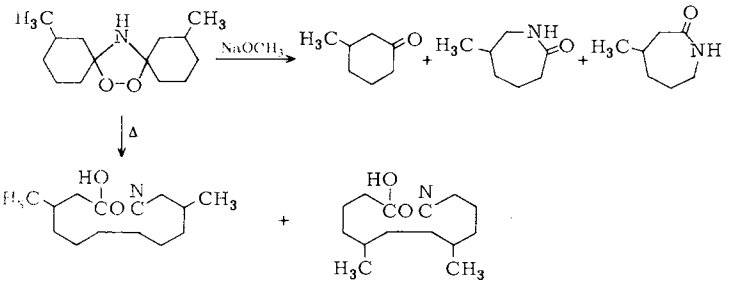


Thermal decomposition of *(1)* in the liquid phase gave a complex mixture of products, including cyclohexanone, caprolactam, and C_{12} compounds, whereas pyrolysis in the vapor phase at 350—600 °C under reduced pressure gave *ca.* 60% yields of C_{12} compounds together with caprolactam (*ca.* 20%) and cyclohexanone (< 30%). The nature of the C_{12} compounds varied with the temperature and residence time; at 350—400 °C the major product was decanedicarboximide *(85)*, and at higher temperature 11-cyanoundecanoic acid *(86)*. By-products, in minor amounts, included the monoamide of dodecanedioic acid, dodecanediamide, dibutylsuccinimide *(87)*, 2-butyl-7-cyanoheptanoic acid *(88)*, 7-cyanoundecanoic acid *(89)*, hexanamide, and a compound thought to be 1-hydroxy-*N*-hexanoylhexanamide *(90)*, which dehydrates to 5-butyl-2-pentyl-4-oxazolinone *(91)* on distillation; the formation of several of these C_{12} by-products involves 1,5-radical rearrangements.

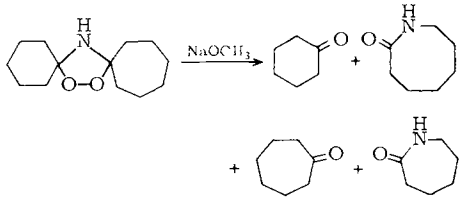


Other symmetrical cyclic peroxyamines derived from cyclic ketones behaved in a similar fashion on reaction with

sodium methoxide and on pyrolysis, although where isomeric lactams or cyano-acids were possible by rearrangement in two ways both were present in the products[5].

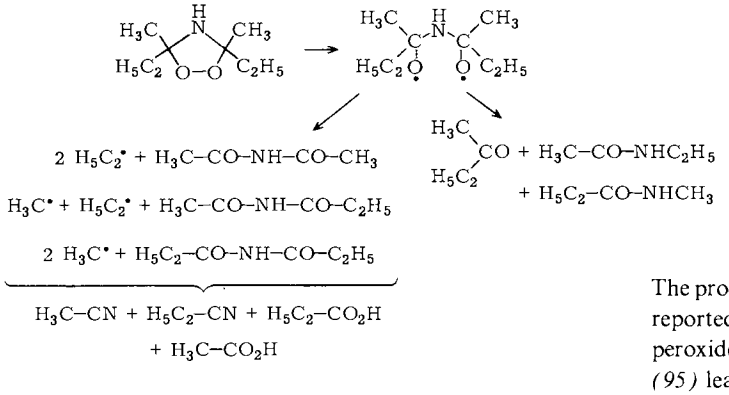


Unsymmetrical 1,2,4-dioxazolidines underwent base-catalyzed and pyrolytic decompositions to give mixtures of ketones, lactams, and cyano-acids.



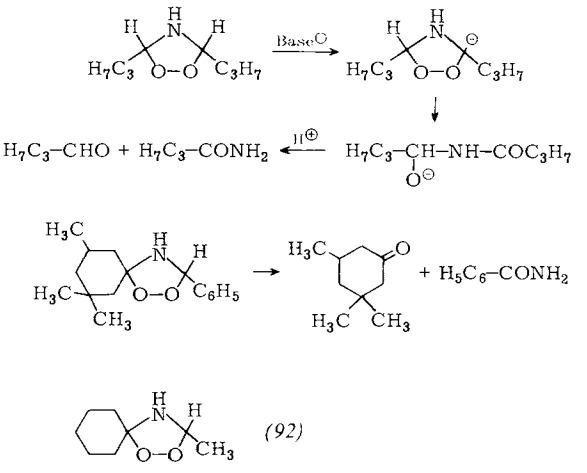
However, the unsymmetrical dioxazolidines *(83)*, R^1 and/or R^2 = aryl; R^3, R^4 = —$(CH_2)_5$—, obtained by imine oxygenation, gave a much more complex mixture of compounds on decomposition. Thus, although reaction with sodium methoxide afforded caprolactam (low yields) and benzophenones, varying amounts of benzanilides, cyclohexanone, benzonitriles, and diarylmethanols were also formed[5,11].

Pyrolysis of cyclic peroxyamines derived from acyclic ketones caused a fundamentally related decomposition to give ketones, amides, nitriles, and acids; the nitriles and acids were derived from imides, in turn produced from the diradicals by loss of alkyl radicals[6].



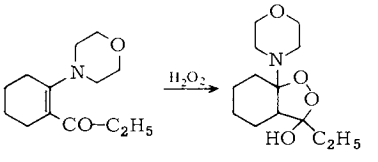
The dioxazolidines derived from aldehydes have a secondary-tertiary or disecondary peroxide system, and, in consequence, are easily decomposed by bases (*e.g.* triethylamine), by a normal Kornblum-De La Mare mechanism, to yield a carbonyl compound and amide.

Surprisingly, although 3,3-pentamethylene-5-methyl-1,2,4-dioxazolidine *(92)* similarly gives cyclohexanone and acetamide on treatment with triethylamine, it afforded a moderate amount of caprolactam on addition to a solution of lithium chloride in boiling methanol[4].

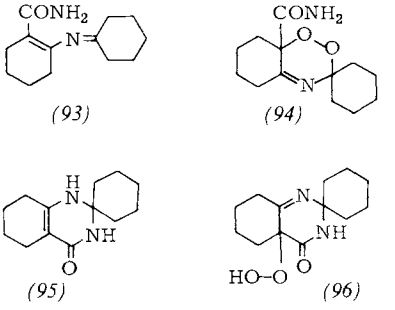


9. Miscellaneous Cyclic Peroxyamines and -imines

The addition of hydrogen peroxide to enamines to form α-peroxyamines has already been mentioned (Section 6.1)



but when the enamine also had a carbonyl group suitably positioned, intramolecular cyclization of the intermediate α-hydroperoxyamine led to a cyclic peroxide where the nitrogen was not part of the ring[12].



The product of reaction of cyclohexanone with urea, earlier reported to have the structure *(93)* and to give the cyclic peroxide *(94)* on autoxidation[13], is now thought to be *(95)* leading to a hydroperoxide *(96)*[14].

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Sesquiterpenes

By Gerhard Rücker[*]

Of the 4000 or so terpenoid natural products known today, whose carbon skeleton can be divided up into isopentane units by the "isoprene rule" (C_{10}, monoterpenes; C_{15}, sesquiterpenes; C_{20}, diterpenes; C_{25}, sesterterpenes; C_{30}, triterpenes; steroids; carotenoids; polyprenes), the sesquiterpenes, numbering about 1000, represent the largest single class. According to the well founded concepts developed in recent years for the biogenesis of their highly diverse carbon skeletons, the present report is divided into nine sections dealing respectively with farnesanes, bicyclofarnesols (drimanes, iresanes), bisabolanes, cadinanes, humulanes and caryophyllanes, germacranes, "hydroazulenes", selinanes and eremophilanes, and maalianes and aristolanes. Further groups of sesquiterpenes can be derived from each of these structural types.

1. Introduction

The chemistry of the sesquiterpenes with their 15 carbon atoms—corresponding to three isopentane units—arranged in an acyclic or mono-, bi-, tri-, or tetracyclic skeleton has undergone a period of rapid development during the past two decades following the introduction of chromatographic separation techniques and physical methods of structural analysis. In 1953 about 16 sesquiterpene skeletons were known corresponding to about 30 compounds, in 1964 the respective figures were 40 and

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300, and in 1971 100 and 1000. Sesquiterpenes having the same carbon skeleton are classified as a single group. The farnesanes, bisabolanes, cadinanes, humulanes, germacranes, selinanes number among the larger and better known groups of sesquiterpenes (cf. Fig. 1).

The sesquiterpenes, which occur primarily in higher plants—less frequently in lower plants and in the animal kingdom (*e.g.* in insects)—are often steam volatile, and comprise not only mostly unsaturated hydrocarbons (including some alkynes) but also alcohols, ketones, aldehydes, and carboxylic acids. They may also contain three- to seven-membered ether rings and furan rings. Chlorine- and bromine-substituted sesquiterpenes, as well as about 25 nitrogen-containing compounds with 15 C atoms (sesquiterpene alkaloids) isolated predominantly from *Nymphaeaceae* also deserve mention. Compounds with only 12 or 14 carbon atoms (norsesquiterpenes) can also be derived from certain sesquiterpenes.

The sesquiterpene lactones occurring in *Compositae*, and also in other plant families, have attracted particular interest. The first compound of this class, α-santonin[1], which was isolated in crystalline form in 1830, is still the object of intensive study[2]. So far about 300 sesquiterpene lactones are known; worthy of particular mention are the germacranolides[3,4], guaianolides[3-5], pseudoguaianolides[3,6,7], selinanolides (≡ eudesmanolides)[8], and eremophilanolides[4]. Most of them are saturated or α,β-unsaturated γ-lactones. Apart from a few δ-lactones, only two β-lactones (anisatin, neoanisatin)[9] have been found. A trilactone, bilabolide[10], is also known alongside about 25 dilactones.

In addition to the isolation and structural elucidation of numerous new compounds recent advances in sesquiterpene chemistry have included a better knowledge of the stereochemistry of the molecules, their reactivity and rearrangements, and their biogenesis. In this connection the outstanding successes achieved in the synthesis of sesquiterpenes should be emphasized[*]. Several earlier structural assignments have been corrected by syntheses and application of modern physical methods[4]. Thus the "vetivanes", formerly regarded as hydroazulenes, proved to be spirocyclic agarospiranes or eremophilanes with a decalin skeleton[12]. The detection of sesquiterpenes with toxic and interesting biological properties, *e.g.* cytotoxic activity[15], also deserves mention (for reviews see refs. [13—15]). In the present brief progress report most of the studies on sesquiterpenes published in the past two decades have had to go without mention; such are included as references in the publications cited below and in reviews[3-8,11,13,15-19].

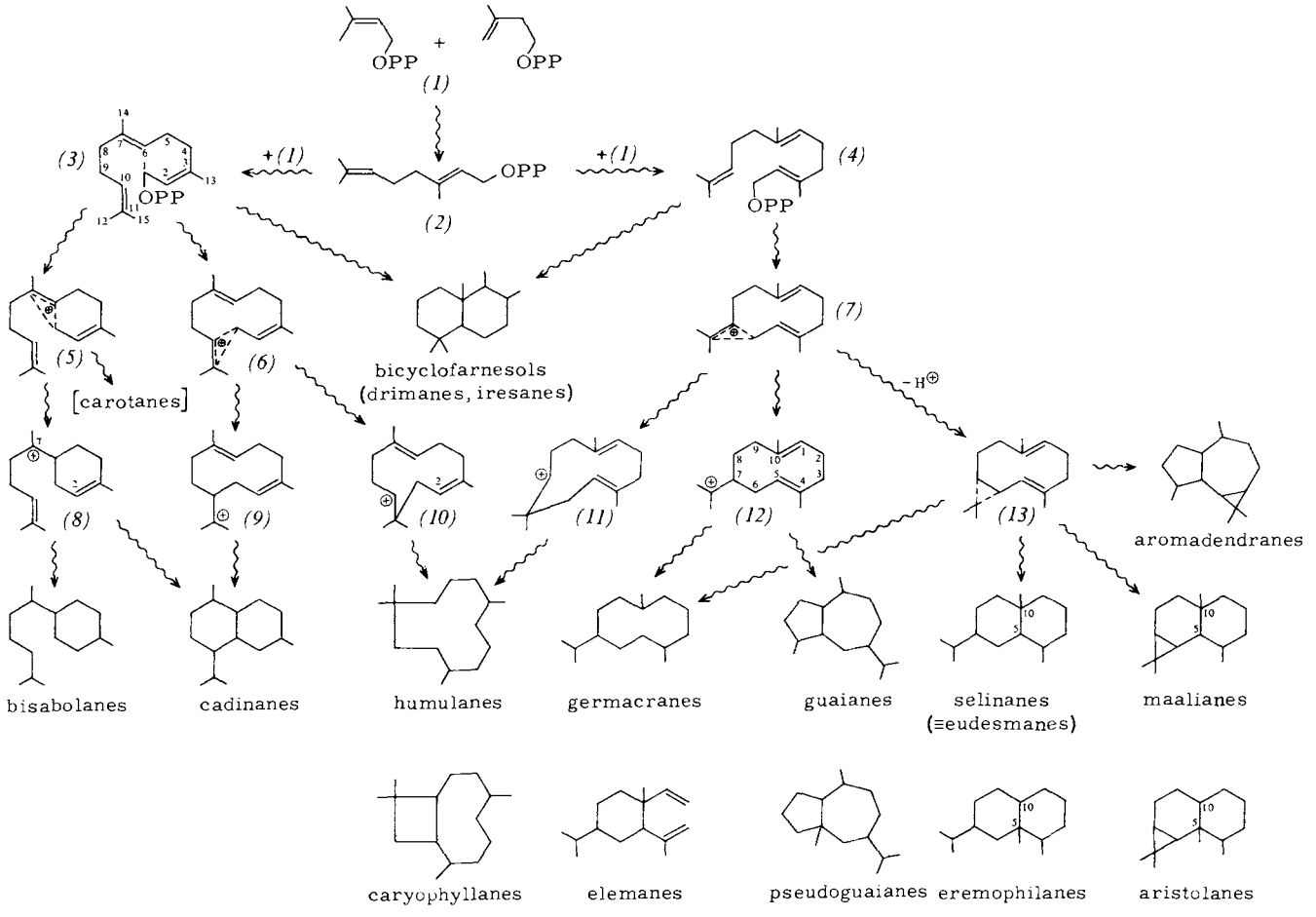


Fig. 1. Biogenesis of the sesquiterpenes. Wavy lines in this and the following figures signify biogenetic transitions. The basic skeletons are generally shown without multiple bonds.

[*] For a review see ref. [11]; for examples refs. [25, 33, 37, 38, 50, 64, 69, 82, 111, 117, 126, 130, 131, 135, 138, 145, 151, 165, 167, 173].

It was not easy to hit upon a reasonable and comprehensive scheme for a discussion of sesquiterpenes. The present report is essentially arranged in line with biogenetic considerations (Fig. 1). The nine sections deal with biogenetically related, or interconvertible, groups of sesquiterpenes. Reviews have appeared on the biogenesis of these compounds[11, 13, 17, 18, 20].

According to *Ruzicka* and *Hendrickson*, 2-*cis*-6-*trans*-farnesyl pyrophosphate *(3)* or the corresponding 2-*trans*-6-*trans* compound *(4)* is regarded as the biological precursor of almost all sesquiterpenes; it is formed from acetyl coenzyme A *via* mevalonic acid, isopentenyl pyrophosphate *(1)*, and geranyl pyrophosphate *(2)* (Fig. 1). For steric reasons, a 2-*trans*-6-*cis*-farnesyl-, a 2-*cis*-6-*cis*-farnesyl-, or a nerolidyl precursor has to be assumed for a few sesquiterpenes. Removal of the pyrophosphate group from *(3)* or *(4)* yields carbocations whose formulation as nonclassical cations *(5)* and *(6)* or *(7)* explains their cyclization to two cyclic cations each [*e.g.* *(9)* and *(10)* from *(6)*; *(11)* and *(12)* from *(7)*]. These can afford most of the sesquiterpenes by processes such as 1,2- or 1,3-hydride shifts, electronically and sterically controlled cyclizations with the two remaining double bonds ("Markownikoff" and "anti-Markownikoff cyclizations"), Wagner-Meerwein rearrangements, and 1,2-methyl shifts. Considerable significance attaches to the biogenetic formation of diastereoisomers and enantiomers. It should however be noted that many hypotheses regarding the biosynthesis of sesquiterpenes that are based on structure, stereochemistry, and reactivity still require experimental proof *in vivo*[13, 20].

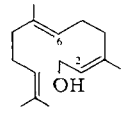
The future of terpene research will still be concerned primarily with the isolation and structural elucidation of new compounds which could be important as missing biosynthetic links, as biologically active substances, or as reactants for the study of chemical problems. The sesquiterpenes throw up problems of a largely stereochemical nature. The course of their numerous rearrangements provides information about relationships between stereochemical and electronic factors and the reactivity of the compounds. The chemistry of nonclassical carbocations has also profited from work on sesquiterpenes. The photochemistry of the sesquiterpenes is still in its infancy. Syntheses of sesquiterpenes nearly always have to be carried out stereoselectively; they can contribute to the solution of problems in preparative chemistry.

Knowledge of reactivity, photochemistry, and syntheses stimulate research into sesquiterpene biogenesis, a field that will become increasingly important in the future. The aim is to elucidate the formation of the numerous carbon skeletons and to obtain information about the reasons behind the frequently complex stereospecific biosynthetic pathways that could also be of interest for the biogenesis of other natural products. In this connection, importance also attaches the site of formation and of deposition of the sesquiterpenes in plants and to their distribution throughout the plant and animal kingdoms. The biological properties of some sesquiterpenes show that they are not merely metabolic "waste products". For instance, they are of significance as plant growth substances, growth regulators, and sex attactants of fungi. Others function as the juvenile hormones essential for normal development of insects or occur as components of insect secretions. These aspects have opened up an area of sesquiterpene research that is of potential interest, *e.g.* for the solution of practical problems of influencing the growth of cultivated plants and in plant protection.

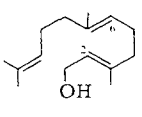
Sesquiterpenes can provide impetus to drug research too. The starting point of such work is the pharmacological effects determined so far for a relatively small number of compounds. They include cytotoxic, antibiotic, fungistatic, virostatic, anthelmintic, antiphlogistic, and sedative properties, thus covering a fairly broad spectrum. Considerable uncertainty still surrounds the extent to which the sesquiterpenes contribute to the manifold and frequently unspecific action of the essential oils in which they occur. Mention should be made here of the importance of sesquiterpene research for the chemistry of essences and of aromas and flavors.

2. Acyclic Sesquiterpenes (Farnesanes)

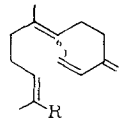
The first sesquiterpene whose structure was correctly determined (1913)[21] is the widely distributed 2-*trans*-6-*trans*-farnesol *(4a)*. The 2-*cis*-6-*trans* compound *(3a)* has also been found in essential oils[22]. Like other natural and synthetic compounds derivable from farnesane and bisabolane (Fig. 2), *(4a)* and *(3a)* have a juvenile hormone action on insects[13, 23]. The saturated parent hydrocarbon farnesane has also been found to occur in Nature, as have monounsaturated farnesenes. Essential oils frequently contain the fourfold unsaturated 6-*trans*-β-farnesene [(*E*)-β-farnesene] *(14)*[24, 25]. Of the four *cis-trans* isomeric α-farnesenes, which have all been synthesized, only two have so far been found in Nature[25], (*E*,*E*)-α-farnesene *(15)* and (*Z*,*E*)-α-farnesene *(16)*. The all-*trans* aldehydes β- *(17)* and α-sinensal *(18)* occur in *Citrus* species[26].



(3a)



(4a)



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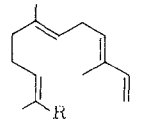
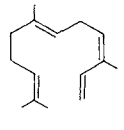
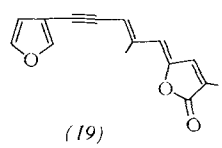
(17), R = CHO



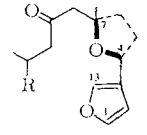
(15), R = CH_3
(18), R = CHO



(16)



(19)



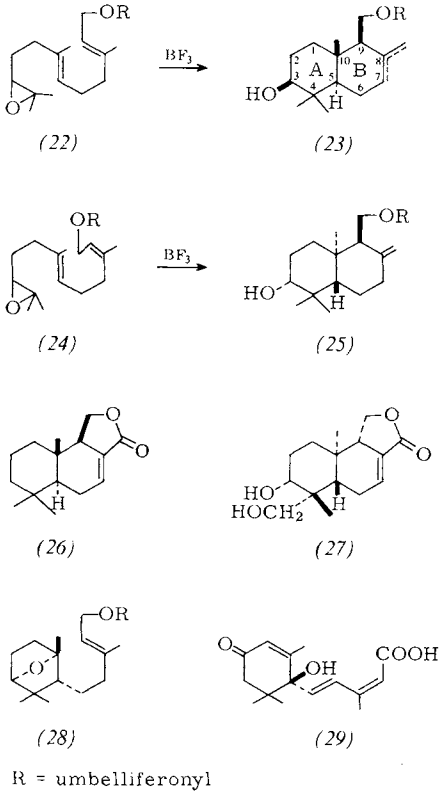
(20), R = CH_3
(21), R = CH_2OH

Only one lactone has so far been discovered in the farnesane group, *viz.* freelingyne *(19)* containing a triple bond and a furan ring[28]. The hepatotoxic substances from *Myo-*

porum species and from sweet potatoes infected with fungi [(−)-ngaione, (+)-ngaione (≡ipomeamarone) *(20)* and ipomeamaronol *(21)*], having a furan ring bridging C-1 and C-13[29] and a tetrahydrofuran ring[27] between C-4 and C-7, number among the farnesanes. Farnesanes with two furan rings are also known[30].

3. Bicyclofarnesols (Drimanes, Iresanes)

The drimanes, *e.g. (23)* and *(26)*, and iresanes, *e.g. (25)* and *(27)*, constituting the small group of the bicyclofarnesols, possess enantiomeric skeletons. Their biogenesis is assumed to involve direct *trans*-antiparallel cyclization of farnesyl pyrophosphate (Fig. 1), *(3)* possibly representing the precursor of the drimanes and *(4)* that of the iresanes[20]. Accordingly, the epoxide of *trans,trans*-farnesyl umbelliferonyl ether *(22)* cyclizes in the presence of BF_3 to give drimenol umbelliferonyl ether *(23)*[31]. Under the same conditions the epoxide of *trans,cis*-farnesyl umbelliferonyl ether *(24)* afforded a very low yield of farnesiferol A *(27)* having an iresane skeleton[31,32]. The umbelliferonyl ether of *(3)*, umbelliprenin, was isolated from *Umbelliferae* (*e.g. Ferula* species). Sterically the skeleton of the drimanes corresponds to rings A and B of most di- and triterpenes. The opposing "unusual" steric arrangement of the iresanes is found in only a few higher terpenes. Most drimanes and iresanes are unsaturated γ-lactones with the lactone ring in the 8,9 position [*e.g.* cinnamolide *(26)* and iresine *(27)*][33,34]. Farnesiferol C *(28)*[32], which has been known for some time, and the plant growth regulating abscisic acid (≡abscisin II≡dormin) *(29)*[35,36] from young cotton fruit and sycamore leaves can be derived from *(3)* or *(4)* by simple cyclization[20].



(22) *(23)*

(24) *(25)*

(26) *(27)*

(28) *(29)*

R = umbelliferonyl

4. Bisabolanes and Related Sesquiterpenes

Precursors having the monocyclic skeleton of bisabolane—*(8)*, *(40)*, *(41)*, *(42)* (Figs. 1 and 2)—have to be considered for the biogenesis of many sesquiterpenes[20]. The bisabolane group is known to contain numerous hydrocarbons, alcohols, ketones, aldehydes, and carboxylic acids. Only β-bisabolene *(30)* will be mentioned as an example. The insect juvenile hormone (+)-juvabione *(35)* was found to deviate in the stereochemistry of its side chain[23,37]. Bisabolanes having aromatic or quinonoid six-membered rings and with tetrahydrofuran or lactone rings are also known.

Several small groups of sesquiterpenes representing isoprenologous monoterpenes can be derived from the cation *(8)* (Figs. 1 and 2) by deprotonation and cyclization. These include l-sirenin *(39)*, an isoprenologous carene (sesquicaranes), the sex attractant of the female gametes of several fungi[38]. α-Bergamotene [*(36)* or *(37)*] is an isoprenologous α-pinene, and β-bergamotene *(38)* an isoprenologous β-pinene. Synthetic studies[39] have shown that the isoprenoid side chain and the cyclohexene ring may be mutually "*trans*" or "*cis*" oriented [*(36)* or *(37)*] in natural α-bergamotene, while β-bergamotene occurs only as the "*trans*" compound *(38)* in Nature. The biogenesis of the antibiotic and cytostatic fumagillin *(34)* from *Aspergillus fumigatus*[13,14] is assumed to involve cleavage of the cyclobutane ring in *(38)*[20]. Cyclization, Wagner-Meerwein rearrangement, and deprotonation of the cation *(8)* can yield two isoprenologous camphenes, the bicyclic β-santalene *(31)*[40] and the tricyclic α-santalene *(32)*[7], which occur alongside other santalenes in Indian sandalwood oil[41]. Isoprenologous bornanes such as campherenol *(33)* are related to the bisabolane cation *(8)*[42].

The discovery of the diketone acorone *(44)* as the first sesquiterpene having a spirocyclic carbon skeleton by *Šorm et al.*[44] attracted acute interest and led to the isolation of further acoranes. Cyclization of the cation *(41)* [or *(40)*] is invoked to explain the biosynthesis of the [4.5]spirocyclic sesquiterpenes. Various stereoisomeric forms of the skeleton can apparently arise depending upon the steric course of the reaction: for instance, cation *(45)* which is regarded as a precursor of α-acorenol *(49)* and deviates sterically from acorone *(44)*. A differently substituted [4.5]spirocyclic ring system is found in the agarospiranes which are biogenetically related to the selinanes (Fig. 7).

Cation *(45)* can be transformed into the tricyclic cedranes, *e.g.* (−)-α-cedrane *(50)* by renewed ring closure[43] and is regarded as an intermediate of the acid-catalyzed conversion of *(49)* into *(50)*[43]. The small group of the cedranes[45,46] embraces hydrocarbons, *e.g. (50)*, alcohols, and carboxylic acids occurring in *Juniperus* species, cedarwood oils, and in the basic hydrolyzates of shellac, which is well known to be secreted by the insect *Lacifer lacca*[47].

Biogenetic precursors of the chamigranes such as *(52)*[48] having a spiro[5.5]undecene structure *(46)* and the cuparanes *(43)* can be formed from cation *(42)* by cyclization[20,46]. The chamigrane cation *(46)*, whose biogenesis by direct cyclization of *(3)* or *(4)* analogous to the formation of the bicyclofarnesols is also conceivable[49], is also

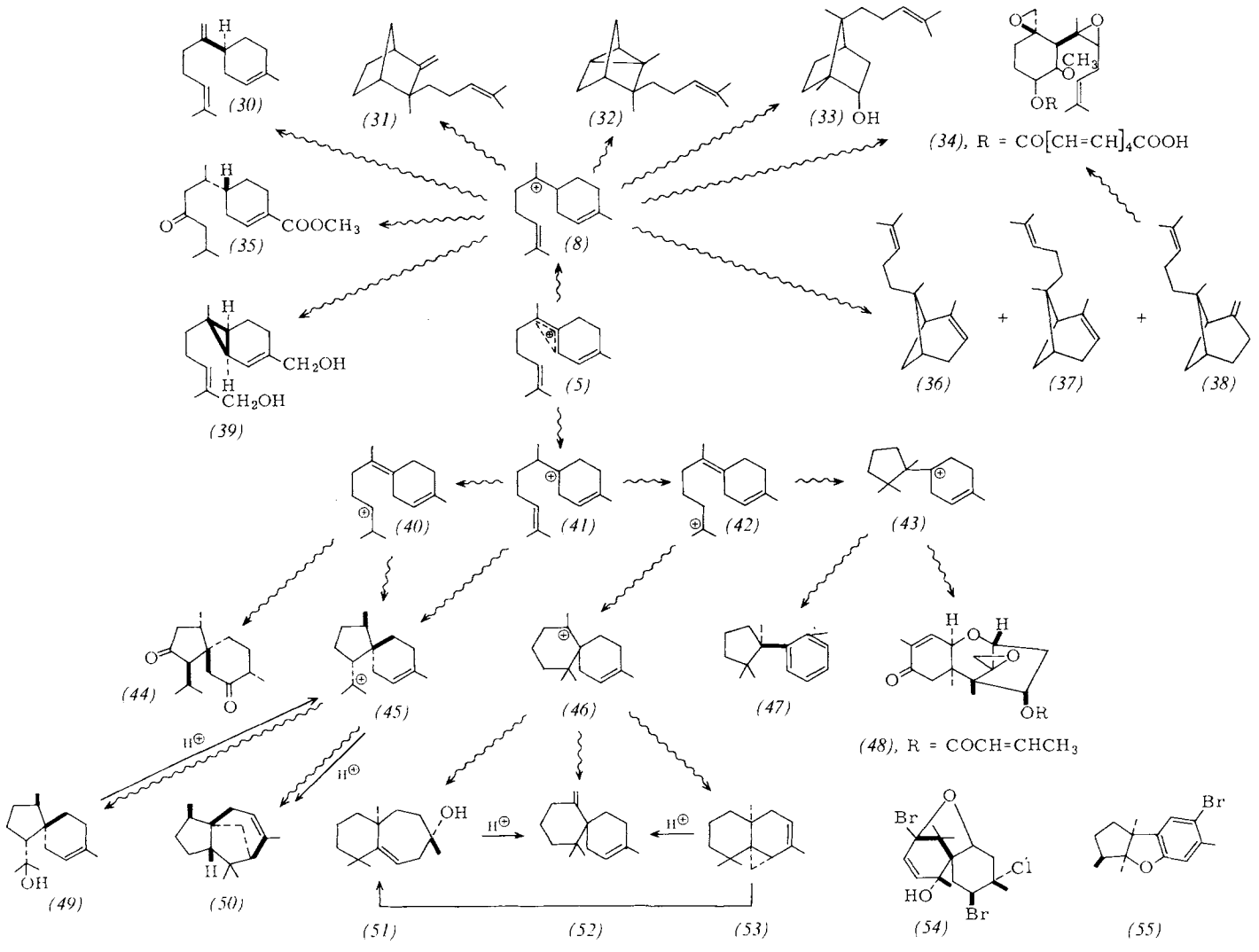


Fig. 2. Bisabolanes and related sesquiterpenes.

viewed[20] as a precursor of widdranes such as *(51)* (widdrol) and thujopsanes such as *(53)* (thujopsene)[46,50]. Acid-catalyzed transitions have been observed between these small groups of related sesquiterpenes, *e.g.* from *(51)* and *(53)* to β-chamigrene *(52)*[48] or from *(53)* to *(51)*[51]. A recent discovery was the chamigrane derivative pacifenol *(54)*, the first sesquiterpene to contain both chlorine and bromine[52]. Nearly all the cuparanes, which are mainly isolated from *Cupressaceae*, *e.g.* cuparene *(47)*, contain an aromatic ring[46]. Algae, fungi, and molluscs afforded substances such as aplysin *(55)* exhibiting a modified substitution of the parent system[53] (lauranes) which may also contain chlorine or bromine, as well as an additional ether ring, and, like *(54)*, are regarded as detoxification products of halogenated pesticides[52]. The trichothecanes, *e.g.* trichothecin *(48)*, isolated as cyclic esters (roridins, verrucarins) from microorganisms and of interest owing to their antibiotic properties[13,54], are derivable from cation *(43)*.

5. Cadinanes and Related Sesquiterpenes

Sesquiterpenes having a 1,7-dimethyl-4-isopropyldecalin skeleton (Figs. 1 and 3) are designated cadinanes, and frequently also as cadalanes, because they afford the naphthalene derivative cadalene on dehydrogenation with sulfur or selenium. The cadinanes, which all contain an α-isopropyl group, can be divided into four types according to the stereochemistry of the ring linkage (Fig. 3): the true cadinanes, *e.g. (57)* [(+)-γ-cadinene] and the bulgaranes, *e.g. (58)*[55] [(−)-ε-bulgarene], display a *trans* linkage of the two cyclohexane rings, and the muurolanes, *e.g. (59)* [(−)-α-muurolene][56], and amorphanes, *e.g. (60)* [(−)-γ-amorphene][56] a *cis* linkage.

Cyclization of the bisabolane cation *(8)* or the germacrane cation *(9)*[57] (Figs. 1 and 3) or of a 2-*cis*-6-*cis*-farnesyl precursor[20] is assumed to account for the biogenesis of these four stereochemical variants of the dimethylisopropyldecalin system. Acid treatment of bicyclogermacrene *(13)* (Fig. 1) opens the three-membered ring to give cadinanes[58]. Numerous cadinane hydrocarbons and alcohols (cadinols) have been found in higher and lower[59] plants. Either ring A or both rings of the cadinanes may be aromatic. Furans and *p*- and *o*-quinones with a cadinane skeleton have likewise been found in Nature. Biogenetic formation of the indan derivative oplopanone *(56)* may conceivably proceed *via* ring contraction of an α-cadinol[60]. Relations can also be detected between other sesquiterpenes having an indan-type carbon skeleton and

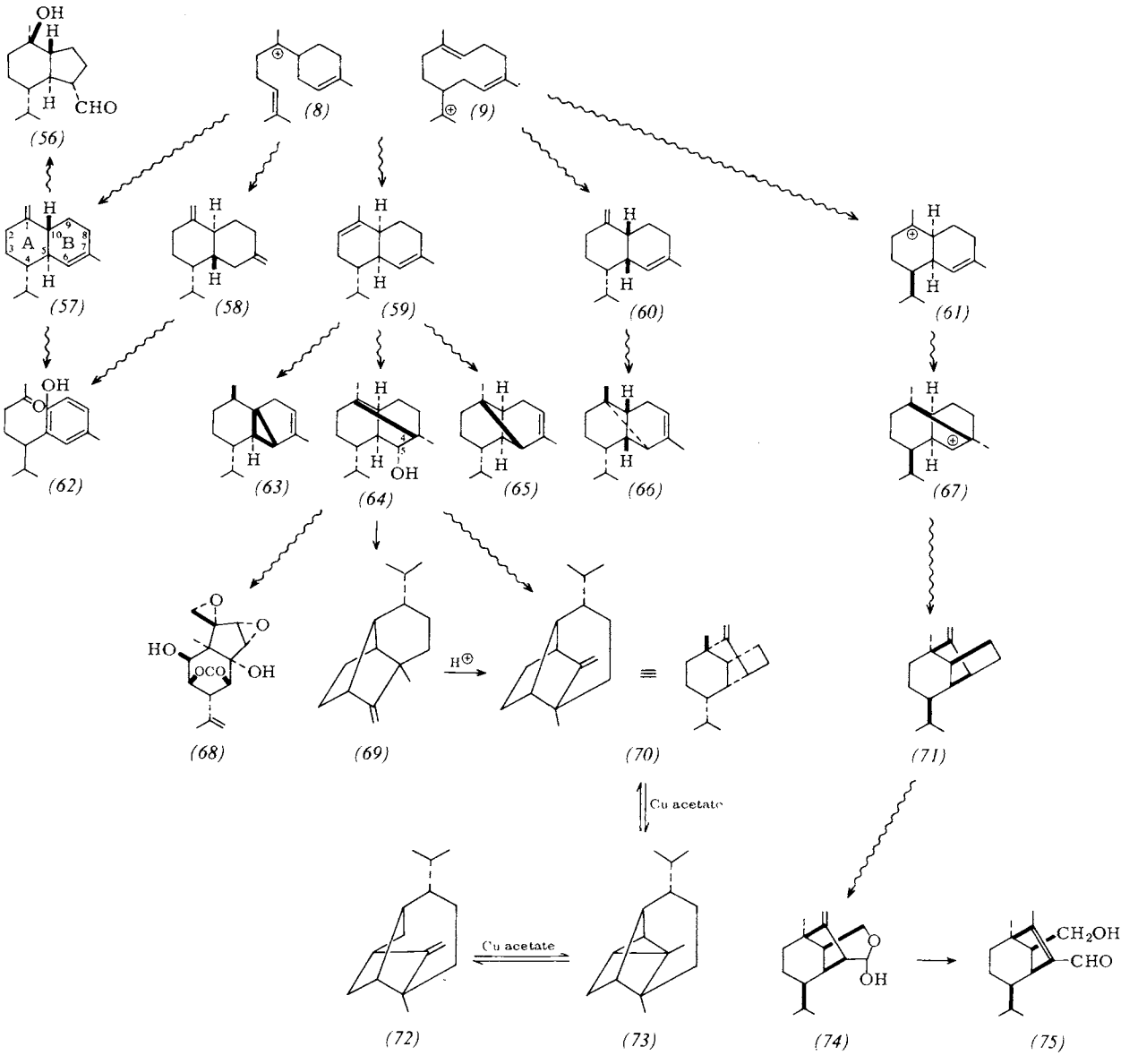


Fig. 3. Cadinanes and related sesquiterpenes.

the humulanes, germacranes, guaianes, selinanes, or eremophilanes[13,20]. Several monocyclic sesquiterpenes having carbon skeletons resembling bisabolane, *e.g.* sesquichamaenol *(62)*[61], are formed by ring cleavage from cadinanes or bulgaranes[20]. The tricyclic cubebanes, *e.g.* *(63)* (α-cubebene)[64], copabornanes *(64)*, and copaanes *(65)* can be derived biogenetically from the *cis*-fused muurolanes *(59)*, and the ylanganes *(66)*[20,62] from the amorphanes *(60)*. Model experiments also suggested that a pigment-sensitized photocyclization of germacrene D *(101)* could be operative in biogenesis of the copaanes *(65)*[63].

(+)-Sativene *(70)* can be derived from the copabornanes *(64)*; it was isolated from *Abies* species[68] and in the presence of copper acetate in acetic acid it equilibrates with cyclosativene *(73)*[68] and isosativene *(72)*[67]. The effect of acid also converts copacamphene *(69)*, which is chemically accessible[67] from *(64)*[69], into *(70)*. Derivatives of cyclocopacamphene, stereoisomeric to cyclosativene at the isopropyl group, were isolated from vetiver oil[70]. Cleavage of the 4,5 bond in *(64)* is considered a possible biogenetic route to the carbon skeleton of the poisonous picrotoxans, *e.g.* *(68)* (tutin)[71].

The grain fungus *Helminthosporium sativum* (≡*Cochliobulus sativum*) produces the helminthosporanes, unstable hemiacetals, *e.g.* *(74)* (prehelminthosporol), which display antiviral activity *in vitro*[13,65]. These compounds are partly converted into the aldehydes helminthosporol *(75)* or helminthosporal on work-up of the plant material[65]. Their biogenesis has been rationalized by invoking cyclization of the cation *(61)* to the "epicopabornane" cation *(67)*, which on deprotonation and rearrangement yields (−)-sativene *(71)*. Compound *(71)* also occurs in the same fungus and is regarded as the immediate precursor of the helminthosporanes[20,66].

6. Humulanes, Caryophyllanes, and Related Sesquiterpenes

The monocyclic humulanes, *e.g.* *(77)* (α-humulene), possess an eleven-membered ring, and the bicyclic caryophyl-

lanes, *e.g. (76)* (β-caryophyllene), a *trans* fused cyclobutane-cyclononane ring system (Figs. 1 and 4). It seemed reasonable to consider the monocyclic cation *(10)* as biological precursor for both groups of sesquiterpenes (Fig. 1)[20], particularly as *(77)* can be converted chemically by ring closure into *(76)*[74,80]. However, the assumption of a common precursor is no longer tenable since it was discovered that all three ring double bonds of α-humulene *(77)* are *trans*[72]. With the exception of caucalol *(79)*[73] which contains a *cis* double bond, the humulanes are considered to arise from the all-*trans* cation *(11)* as biogenetic precursor[20]. α-Humulene *(77)* and β-caryophyllene *(76)*[75–77], first isolated 80 years ago from clove oil, are widely distributed in Nature. In addition, epoxides and alcohols having the same basic skeleton are also known[75,78]. Both *(77)* and *(76)* readily afford tricyclic ring systems (*e.g.* tricyclohumulanes) by molecular rearrangement[74,75,77,79–81]. Starting from *(77)* and proceeding *via* the cation *(78)*[20] one obtains the antibiotically active illudins *(80)*[82,83], marasmic acid *(81)*[83], and hirsutic acid C[84].

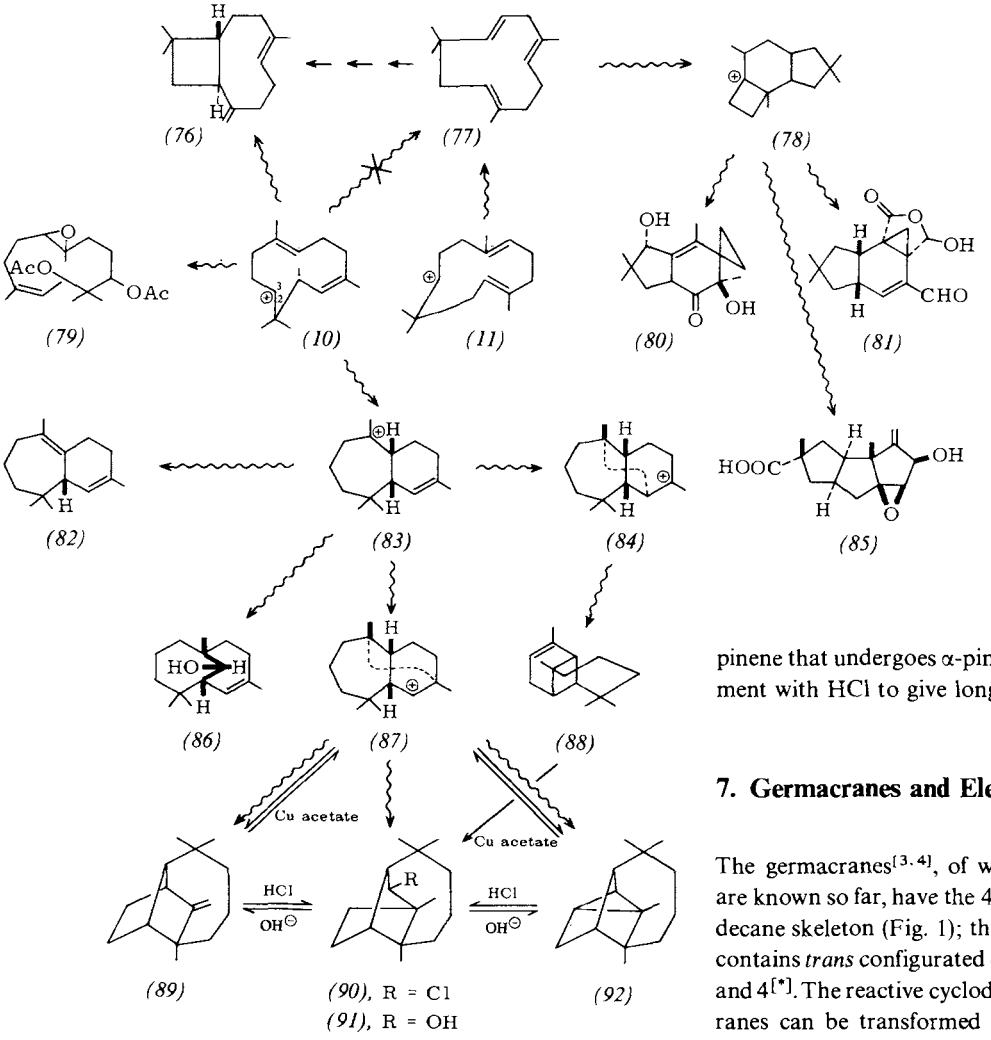


Fig. 4. Humulanes, caryophyllanes, and related sesquiterpenes.

A 1,3 hydride shift and cyclization can transform *(10)* into the cation *(83)* that is of significance as a biogenetic precursor of several small groups of sesquiterpenes[20]. The himachalanes, *e.g. (82)* (α-himachalene) and allohimachalol *(86)*[85], are representatives that have been isolated from cedar oil[86].

The biogenesis of the longifolanes is reported to proceed from *(10) via (83)* to the cation *(87)*[20], from which longifolene *(89)*, longiborneol *(91)*[85], and longicyclene *(92)* are formed. Longifolene *(89)*, which occurs in pine resins, has attracted interest on account of the Wagner-Meerwein rearrangement type reactions involving carbocations[87–89]—which are comparable with the rearrangements of sativene [*(70)*, Fig. 3][67]. In the presence of copper acetate in acetic acid, *(89)* equilibrates *via* the cation *(87)* with isolongifolene[90] and longicyclene *(92)*[67,86,88], which have likewise been isolated from pine species. It is the first naturally occurring tetracyclic sesquiterpene. Treatment with HCl transforms both *(89)* and *(92)* into (+)-longibornyl chloride *(90)*, a homolog of bornyl chloride. Solvolysis of *(90)* regenerates *(89)* and *(92)*[87].

The biogenesis of longipinene *(88)*, which similarly occurs in pine species[91], also proceeds *via* cation *(83)* involving initial cyclization to *(84)*. *(88)* is an isoprenologous α-pinene that undergoes α-pinene-bornyl chloride rearrangement with HCl to give longibornyl chloride *(90)*[87].

7. Germacranes and Elemanes

The germacranes[3,4], of which about 90 representatives are known so far, have the 4,10-dimethyl-7-isopropylcyclodecane skeleton (Fig. 1); the ten-membered ring generally contains *trans* configurated double bonds in positions 1(10) and 4[*]. The reactive cyclodecadiene system of the germacranes can be transformed into mono-, bi-, and tricyclic sesquiterpenes by thermal Cope rearrangements and acid- and light-induced cyclizations (Fig. 5). The germacranes were therefore accorded significance for the biosynthesis of other sesquiterpenes *(20)*, thus stimulating extremely

[*] The molecular skeleton was numbered by analogy with other sesquiterpenes.

intense work on this group. For the same reason relations between reactivity and stereochemistry of the cyclodecadiene system have also attracted attention. Moreover, the

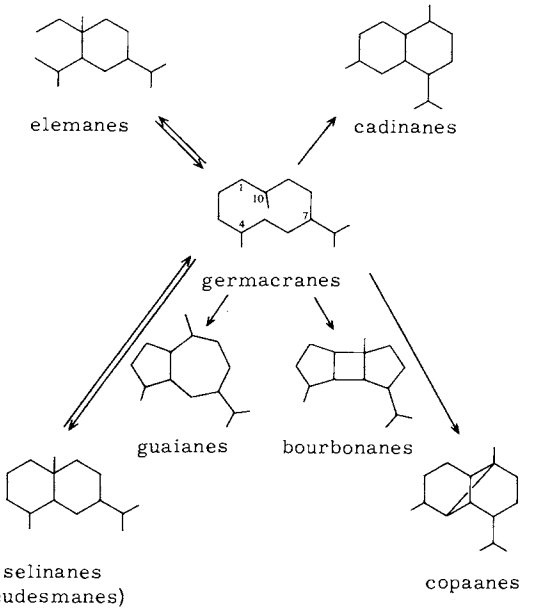


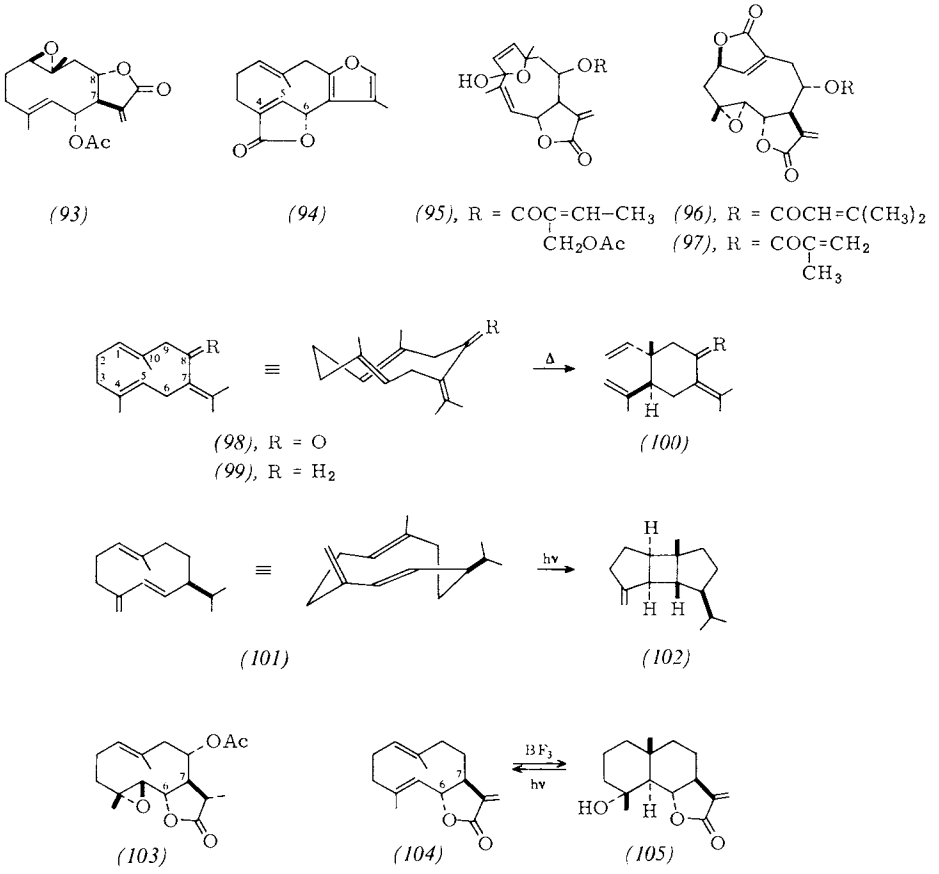
Fig. 5. Rearrangements of germacranes to other sesquiterpenes.

germacranes also include substances with interesting biological properties. Biogenetic formation[20] of the germacrane skeleton from *(4)* (Fig. 1) has been detected by *in vivo* experiments[92].

Most of the germacranes are lactones (germacranolides)[3,4]. Mention should be made of pyrethrosin *(93)*[93,94], the first germacrane derivative to be isolated (1957). In *(93)* the α,β-unsaturated γ-lactone ring is in the 8α,7β position; it can also be in the 6α,7β position, *e.g.* in *(104)*, and more rarely in the 4,6-position, *e.g.* in *(94)* (linderalactone), a representative of the furanogermacranolides. The cyclic hemiketal liatrin *(95)*, like the dilactones elephantin *(96)* and elephantopin *(97)*, possesses cytotoxic properties[13,14,96]. The ketone germacrone *(98)* was the first germacrane found to have no lactone ring[97,98]. Subsequently, the thermolabile germacrenes A to D were discovered to occur in Nature, *e.g.* *(99)* (germacrene B) and *(101)* (germacrene D). Mention should also be made of the bicyclogermacrene *(13)* (Fig. 1) containing a cyclopropane ring[58,99].

An important role is played by the stereochemistry of the cyclodecadiene ring in biogenetic transformations[20] and chemical conversions (Fig. 5) of germacranes into other sesquiterpenes. It could be established for numerous germacranes by X-ray analysis of halogenated derivatives[93] or silver nitrate complexes[98,101,102], by measurement of the nuclear Overhauser effect[103], and by low temperature NMR studies[103]. In the conformation with *syn*-methyl groups in positions 4 and 10 found for most compounds, *e.g.* *(98)*, *(99)*, and *(101)*, the π orbitals are positioned favorably for Cope rearrangements and electrocyclic reactions[100].

Thermal Cope rearrangements[100] of germacranes furnish elemanes[19,58,95,99,100,104], sesquiterpenes having a 1-methyl-1-vinyl-2-isopropenyl-4-isopropylcyclohexane skeleton (Figs. 1 and 5). Apart from a few exceptions[96], the elemanes isolated from essential oils, and also numerous elemane lactones (elemanolides), can be regarded as Cope



rearrangement products of germacranes[58,95,98,104]. Under certain conditions the Cope rearrangement is reversible[19,100,105]; it proceeds stereospecifically. All-*trans*-cyclodecadienes, *e.g. (99)* (germacrene B)[101] are converted into *trans*-elemanes, *e.g. (100)*[99,100], whereas 1(10)-*cis*-4-*trans*-cyclodecadienes form *cis*-elemanes[99]. This rule has been employed in determining the stereochemistry of germacranes[99].

Of the cyclization reactions of germacranes (Fig. 5) we shall first consider the formation of cadinanes in the presence of $H^{\oplus}$ ions[57,58,105,106]. UV-irradiation of germacrane D *(101)* generated *(102)*[107] having the same skeleton as the tricyclic bourbonanes[57] occurring in *Geranium* and *Mentha* species. Under the same conditions, a cyclodecadiene employed as model substance was also transformed into ketones having copaane-type skeletons (Fig. 3)[63]. The formation of guaianes from germacranes, particularly germacrane epoxides[104], has also been reported[58,98,108,109]. Isomerizations of germacranes to guaianes also extend to germacrane lactones[108]. Reports have also appeared of stereospecific[112,113] cyclizations of germacranolides to lactones having a selinane-type skeleton (Figs. 1 and 7)[4,104,11,113,114]. For instance, costunolide *(104)*[102] is converted by the action of boron trifluoride into selinanolide *(105)*[110]; *(105)* regenerated *(104)* in a photochemical process[111].

8. Sesquiterpenes Having a Hydroazulene Skeleton (Guaianes, Pseudoguaianes, and Related Sesquiterpenes)

Several groups of sesquiterpenes possess a hydrogenated azulene[173] skeleton bearing two methyl and one isopropyl groups (Figs. 1 and 6) but differ in the positions of the substituents. The largest group of these "hydroazulenes" comprises the guaianes, with about 100 members, followed by the pseudoguaianes, with about 70. Only a few represen-

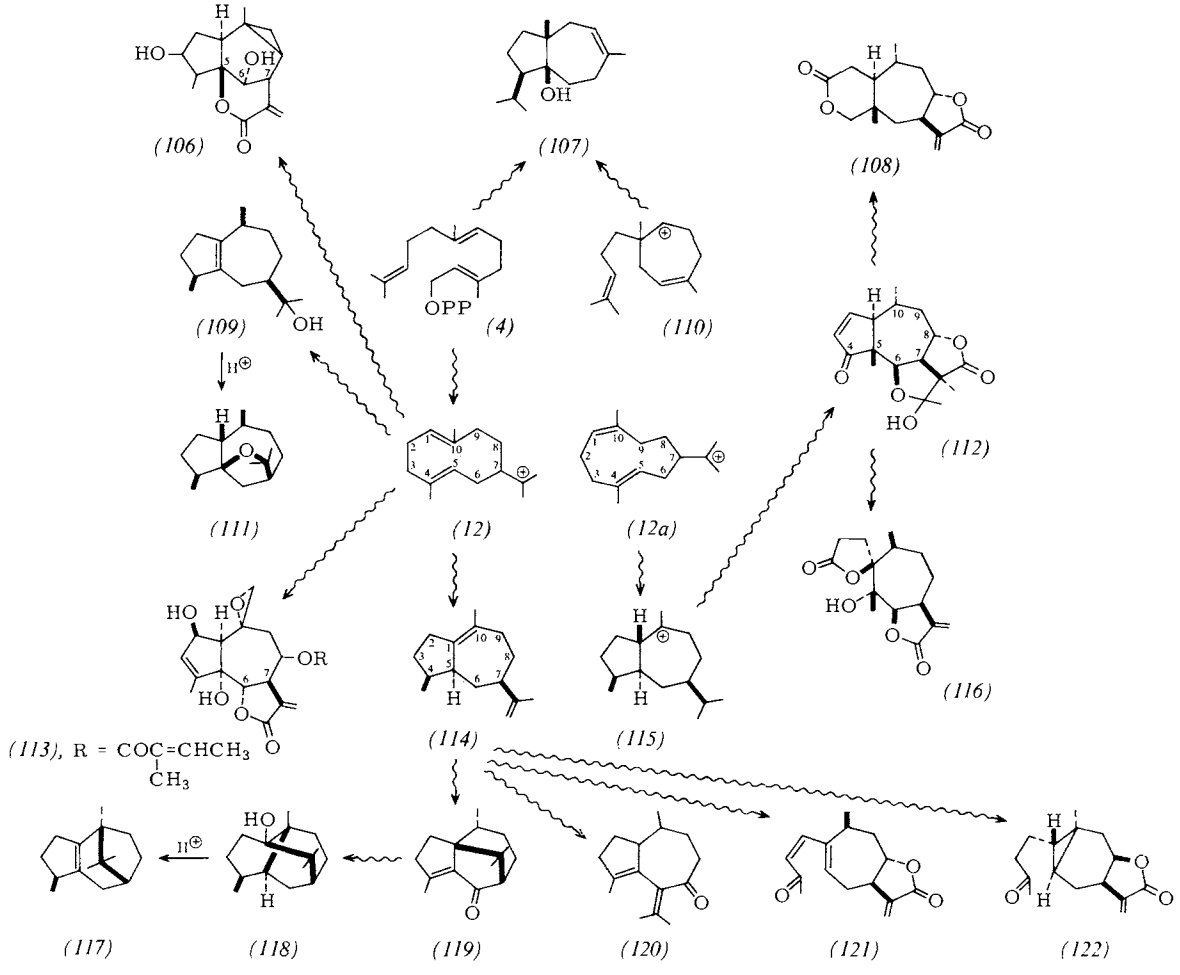


Fig. 6. Sesquiterpenes with a hydroazulene skeleton.

tatives of the carotanes, isopatchoulanes, and zieranes (Fig. 6) have so far become known.

Biogenetically[120], an "anti-Markownikoff cyclization" between C atoms 1 and 5 of cation *(12)* leads to the *cis* linked guaianes (Fig. 6). As examples of this group of sesquiterpenes we can consider α-bulnesene *(114)*[117] and guaiol *(109)*, which undergoes ready conversion into the tetrahydrofuran derivative guaioxide *(111)* by acid-catalyzed ring closure[118]. The guaiane lactones (guaianolides)[3-5] which number about 60 compounds, represent

one of the largest groups of sesquiterpene lactones[3, 5, 8, 18]. Most of them are unsaturated 6α,7β-lactones, *e.g.* euparotin *(113)*. Formation of the lactone ring in positions 7β,8α or 7β,8β is less common. Several guaianolides, *e.g. (113)*, are cytotoxic[96, 119]. Absinthin, obtained from wormwood, is a Diels-Alder adduct of two guaianolides[120]. *(106)* (zaluzanin A) comes from the small group of ivaxillaranes having a tricyclic skeleton[5, 121].

In 1962 *Herz et al.*[122] were able to show that the supposed guaianolide tenulin does not have a methyl group in position 4, but a tertiary one in position 5 *(112)*. This finding constituted the discovery of the first compound having the "pseudoguaiane" skeleton; so far only lactones are known (pseudoguaianolides). They display a pronounced structural variety and occur in *Compositae*[3, 4, 6, 7, 18, 123]. Their generally unsaturated γ-lactone ring is located at 6β,7β, at 7β,8α, or at 7β,8β. The methyl group at C-10 can be in the α or β position. Glycosides of pseudoguaianolides have also been found[124, 125]. 1,5-Cyclization of the cation *(12a)* to give *(115)* is assumed to explain the biosynthesis of the pseudoguaianolides (Fig. 6)[20] which, unlike most guaianes, exhibit *trans* linkage of the two rings. A 1,2 hydride shift and migration of the methyl group from C-4 to C-5 would account for conversion of *(115)* into the skeletons of the two pseudoguaianolides which are diastereomeric in position 10[20].

lides by cleavage of the five-membered ring[8, 15]. As examples we may consider *(121)* (xanthatin), which displays a regulating effect on plant growth[126], and *(122)* (carabrone)[126]. These "derived" sesquiterpenes also embrace dilactones, *e.g. (108)* (vermeerin)[125], and spiro-γ-lactones, *e.g. (116)* (canabrin)[127].

The guaianes are biogenetically related to the small group of isopatchoulanes, *e.g. (119)* (patchoulenone)[129, 130, 133], and the zieranes, *e.g. (120)* (zierone)[128]. Patchouli alcohol *(118)*[131, 132], a compound of unusual structure, is connected with the patchoulanes[11]; it is readily transformed into β-patchoulene *(117)* on treatment with acid. The small carotane group, *e.g. (107)* (carotol)[115, 116], represents a special case with regard to its biosynthesis (Fig. 6). Available evidence suggests either direct cyclization of *(4)*[115] or formation from *(3)* (Fig. 1) by way of *(5)* and *(110)*[20].

9. Selinanes and Eremophilanes

The bicyclic selinanes (≡eudesmanes) and eremophilanes having the basic structure of a dimethyl-7-isopropyldecalin differ only in the position of a tertiary methyl group (Figs. 1 and 7) which is bonded to C-10 in the selinanes and

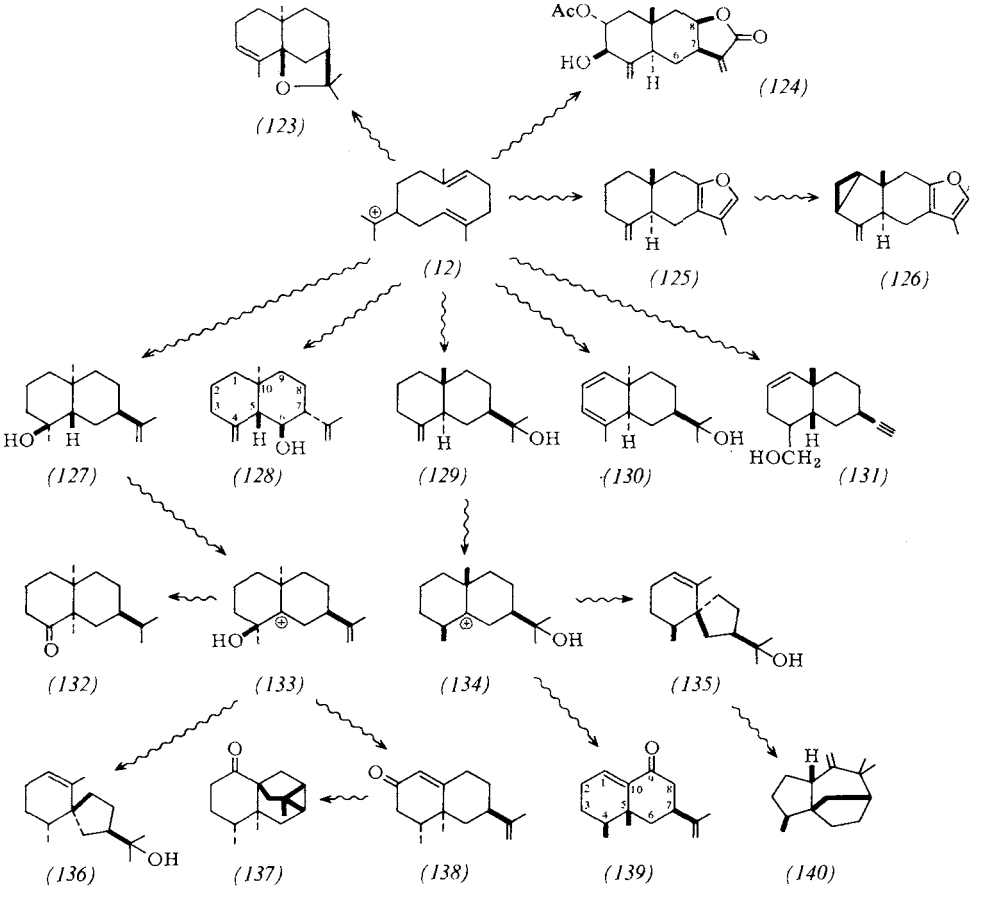


Fig. 7. Selinanes (≡eudesmanes), eremophilanes, and related sesquiterpenes.

Sesquiterpene lactones having a cycloheptane ring and which are designated as xanthinanes and carabranes (Fig. 6) can be derived from guaianolides and pseudoguaianolides to C-5 in the eremophilanes. The skeleton of the eremophilanes cannot be divided into isopentane units like that of the selinanes.

As in the case of the cadinanes (Fig. 3) the selinanes comprise four structural types[134], depending on the mode of ring fusion, whose biogenesis can proceed *via* corresponding conformers of the germacrane cation *(12)*[20,137]. Two of them are *trans*-decalins with the basic structures of (−)-selinane, *e.g. (128)*[140], and the enantiomeric (+)-selinane, *e.g. (129)*[138,139]. The "epi-eudesmanes", *e.g. (130)* [(+)-occidentalol][135], and the chamaecynanes [nor-eudesmanes bearing an ethynyl group, *e.g. (131)*][136] have a *cis*-decalin structure. The same ring linkage as in (−)-selinanes [*e.g. (128)*], but with an opposing steric arrangement of the isopropyl group, is encountered in the agarofurans, *e.g. (123)*[144], and the derivatives of intermedeol *(127)*[141–143].

Atractylone *(125)*[145] is a representative of the furanoselinanes, a group that also includes the lindenanes, *e.g. (126)* (lindenene), which feature a tricyclic skeleton[146]. Approximately 50 sesquiterpene lactones are known to have the selinane-type structure (selinanolides ≡ eudesmanolides)[4,8]. In these compounds γ-lactone ring formation can occur between C-7 and either a 6α-hydroxyl group (santonins[1,2]) or, as in *e.g. (124)* (pulchellin B)[147], an 8β-hydroxyl group.

The selinanes can be regarded as biogenetic precursors for the formation of valeranone *(132)* *via* the cation *(133)*[148]. The valeranes, which are characterized by a *cis*-decalin skeleton, have so far only been found in *Valerianaceae*[148,149]. Two diastereomeric basic structures are known for the [4.5]spirocyclic agarospiranes which are biogenetically related to the selinanes by way of cation *(134)*; the two types are found in hinesol *(135)*[12,151] and agarospirol *(136)*[12,150,152] respectively. Just as the cedranes were derived from the [4.5]spirocyclic acoranes (Fig. 2), the zizaanes (≡ tricyclovetivanes), *e.g. (140)*, can also be regarded as being related to the agarospiranes *(135)*[137], whose biogenesis has been discussed in terms of (+)-γ-curcumene as precursor[153].

The eremophilanes (Figs. 1 and 7) having the basic structure of a 4,5-dimethyl-7-isopropyldecalin have been reviewed in detail[4]. Two sterically distinct types are known: compounds of the "eremophilone type", *e.g. (139)*, have all three side chains in a β-arrangement[154], whereas eremophilanes of the "nootkatone type", *e.g. (138)*, have α-methyl groups[152,155,156]. Both types arise biogenetically from selinanes *via* cations such as *(134)* and *(133)* which undergo a 1,2-shift of the tertiary methyl group[4,7,137,142,143,155]. A spirocyclic intermediate has also been invoked[157] for this biogenetic transformation. Biogenesis of the ishwaranes *(137)* may conceivably involve ring closure by way of the isopropyl group[158].

Eremophilanes, especially lactones (eremophilanolides), have frequently been found in the plants of the *Compositae* family[8]; compounds containing a furan ring (furanoeremophilanes, furanoeremophilanolides) are also encountered.

10. Maalianes and Aristolanes, Aromadendranes

The tricyclic maalianes and aristolanes (≡ calaranes)[159] (Figs. 1 and 8) possess a decalin skeleton with a fused cyclopropane ring. The aristolanes differ from the maalianes, in the same way as the eremophilanes from the selinanes, in the position of the tertiary methyl group. The maalianes (Fig. 8) are biogenetically accessible by cyclization of the cation *(7)* *via* bicyclogermacrene *(13)*

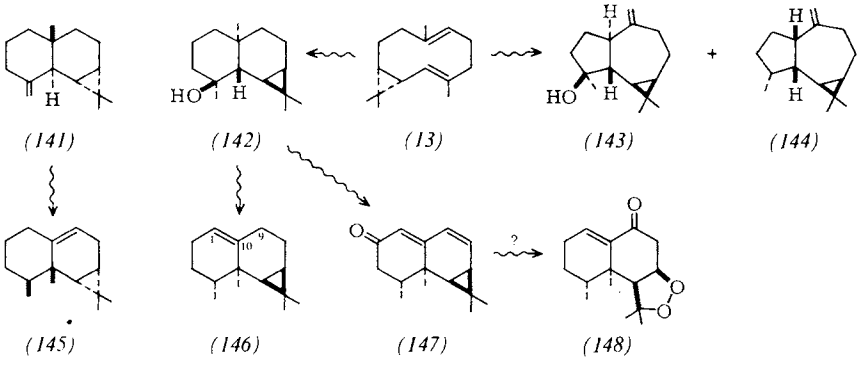


Fig. 8. Maalianes, aristolanes, and aromadendranes.

(Fig. 1)[55]. Apart from maaliol *(142)*[163], compounds are also known with an enantiomeric skeleton, *e.g. (141)* [(+)-γ-maaliene] which could be isolated from the gorgonian *Pseudopterogorgia americana*[164].

Just as the eremophilanes are formed from the selinanes, the aristolanes arise by a 1,2-methyl shift in the maalianes[20,143]. Their biogenesis is thought to proceed from the corresponding selinanes *via* ring closure to give the cyclopropane ring and a 1,2-methyl shift[137]. In addition to 1(10)-aristolene *(146)* (≡ calarene, β-gurjunene)[165] and 9-aristolene, which always occur together[143,159,160,162,166], further aristolane sesquiterpenes were subsequently isolated[160,161,167,168], including the ketone *(147)*[168] whose structure was recently discovered to apply also to the supposed selinane nardostachone[169]. The 1,2-dioxolane derivative nardosinone *(148)* from the valerian *Nardostachys chinensis*[170] is structurally and probably also biogenetically related to the aristolanes. α-Ferulene *(145)* and other enantiomeric aristolanes have likewise been found to occur naturally[164,171].

Both *trans* [*e.g.* spathulenol *(143)*] and *cis* fused compounds [*e.g.* alloaromadendrene *(144)*] are known in the tricyclic aromadendrane series[172]. Supporting evidence for the formation of these sesquiterpenes *via* bicyclo-

germacrene *(13)* is provided by the proton-catalyzed cyclization of this hydrocarbon to give the aromadendrane ledrene[58].

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The Chemistry of Dichloromethylenammonium Salts[1] ("Phosgenimonium Salts")

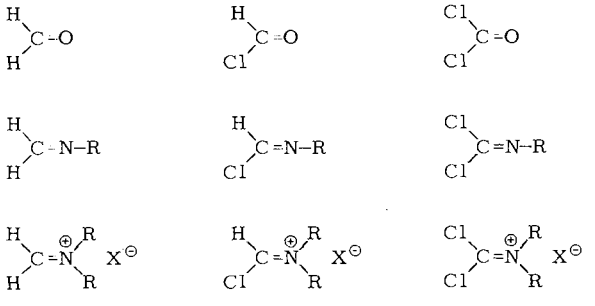
By Heinz Günter Viehe and Zdenek Janousek[*]

Dedicated to Professor Heinrich Hellmann

Dichloromethylenammonium salts, particularly dichloromethylenedimethylammonium chloride, occupy a unique place as stable but reactive building blocks for synthesis. They contain three mobile chlorine atoms activated by an amino group on the same carbon atom. These salts can be regarded as chlorinated Vilsmeier or Mannich reagents and are thus at a higher oxidation level. As in the Mannich or Vilsmeier reaction, the carbon condenses here as an electrophile with formation of C—C or C—hetero atom bonds in a variety that is still far from being exhausted.

1. Introduction

Whereas the chemistry of formaldehyde, the unstable formyl chloride, phosgene, and their imines[2] is well developed, the corresponding imonium salts, *i.e.* the dichloromethylenammonium salts *(3)*, were almost forgotten until the start of our investigations in 1969, though the first compound of this class, *N,N*-diethyl-*N*-dichloromethylenammonium chloride, was described as early as 1959[3].

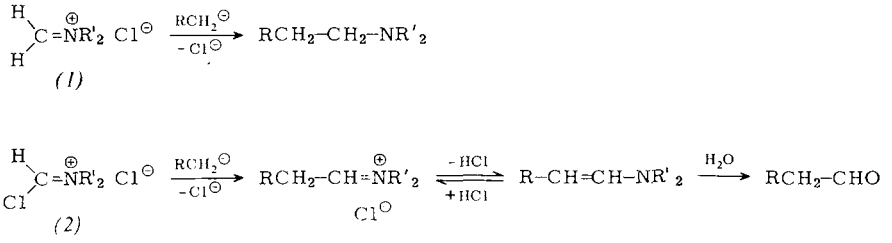


(1) *(2)* *(3)*

This neglect is the more surprising in that the high reactivity of the methylenammonium salts[4] *(1)* has been known for a long time through the Mannich reaction[5]. The chloromethylenammonium salts (Vilsmeier-Haack reagent[6a-6d] [*(2)*, $X^{\ominus}=PO_2Cl_2^{\ominus}$] and Arnold reagent[6e,6f] [*(2)*, $X^{\ominus}=Cl^{\ominus}$]) have also been in use for a long time, though the elucidation of their structures was achieved in part only a few years ago[6g,6h,7].

Mannich reagents *(1)*, as methylenammonium salts, react with nucleophiles by aminomethylation[5]. The Vilsmeier-Haack and Arnold reagents *(2)*, as chloromethylenammonium salts, give corresponding imonium compounds and particularly (by their hydrolysis) aldehydes.

Dichloromethylenammonium salts with tertiary nitrogen are relatively easily obtainable, some even commercially[14]. Dichloromethylenammonium salts with secondary and primary nitrogen can be prepared at least *in situ* from dichloromethylenamine and cyanogen chloride



(1)

(2)

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[cf. *(18)* and *(19)* in Section 2]. These salts are generally strongly electrophilic reagents, which may be compared with the methylenammonium and chloromethylenammonium salts (Mannich reagents and Vilsmeier-Haack and Arnold reagents).

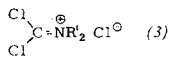
Dichloromethylenammonium salts can substitute the two mobile chlorine atoms and can also react *via* the double bond. Monocondensation leads *e.g.* to amide chlorides *(4)* and their further reaction products such as α-chloroalkenylamines *(5)* and ketene imonium salts *(6)*[8], alkynylamines *(7)*[9a], 1,1-diamino-1-alkenes *(8)*[9b], amidines *(9c)*[9c], and acid and carboxamide derivatives. By dicondensation or tricondensation, *C*-substituted methylamines may be obtained[9d], or else C=N double bonds are formed. For example, cyanamides and the chloroformamidines *(10)* and their salts are formed in this way. Above all, cyclizations become possible, particularly those leading to amino-substituted heterocycles and their derivatives.

Practically all the reactions carried out so far with dichloromethylenammonium salts have yielded new reagents with a value of their own, which will ensure the rapid development of the hitherto neglected chemistry of the dichloromethylenammonium salts (see Table 1).

The neglect of the dichloromethylenammonium salts was due either to their incorrect formulation as trichloromethylamines[3] or to the fact that they were wrongly described as explosive in a review in 1965[10], evidently because of an error in translation from the Russian (the strongly exothermic hydrolysis to diethylcarbamoyl chloride had been described as the only reaction in the Russian article[3]).

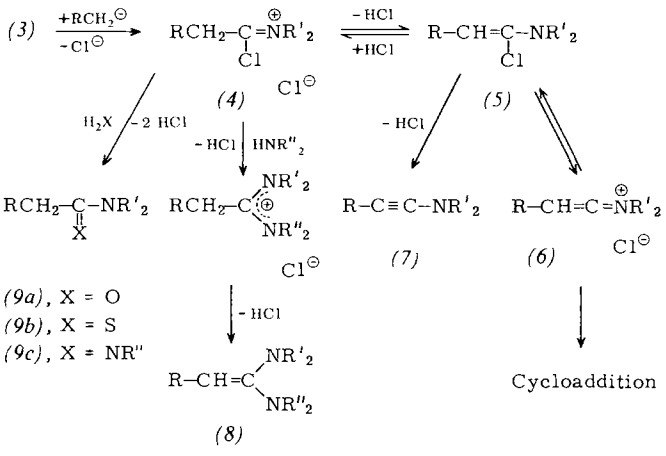
The present article gives a review of this preparatively useful class of compounds, which we originally examined only in order to obtain amide chlorides by a combination of condensation and elimination reactions and also to obtain α-chloroalkenylamines and alkynylamines. In the course of the last three years, however, the aim of our investigations has changed in accordance with the richness of the reaction potential of the dichloromethylenammonium salts. It was useful here to know the analogous reactions of the methylenammonium salts, which were largely investigated by *Böhme*, and of the chloromethyl-

Table 1. Reactions of dichloromethylenammonium chlorides *(3)*.



(3)

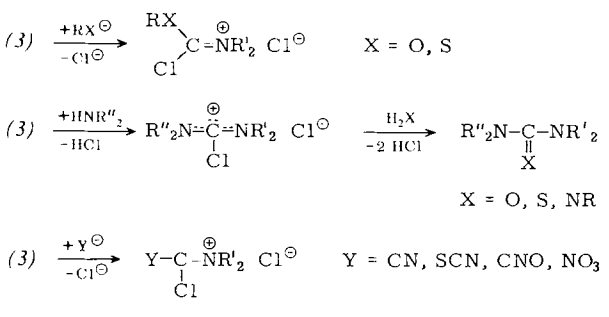
Monosubstitutions with C—C linkage



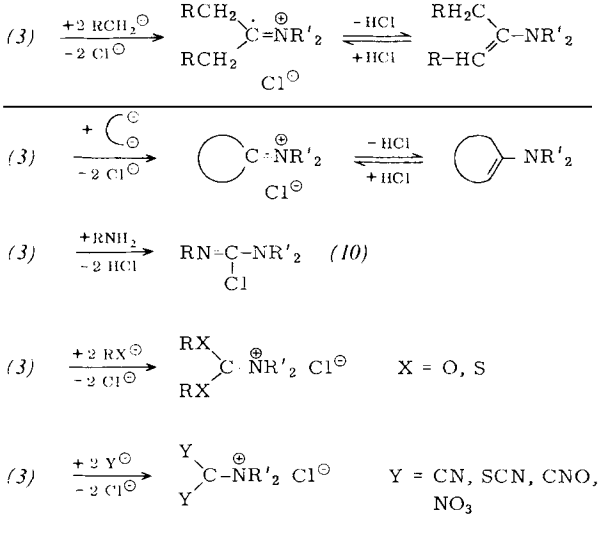
(9a), X = O
(9b), X = S
(9c), X = NR''

Cycloaddition

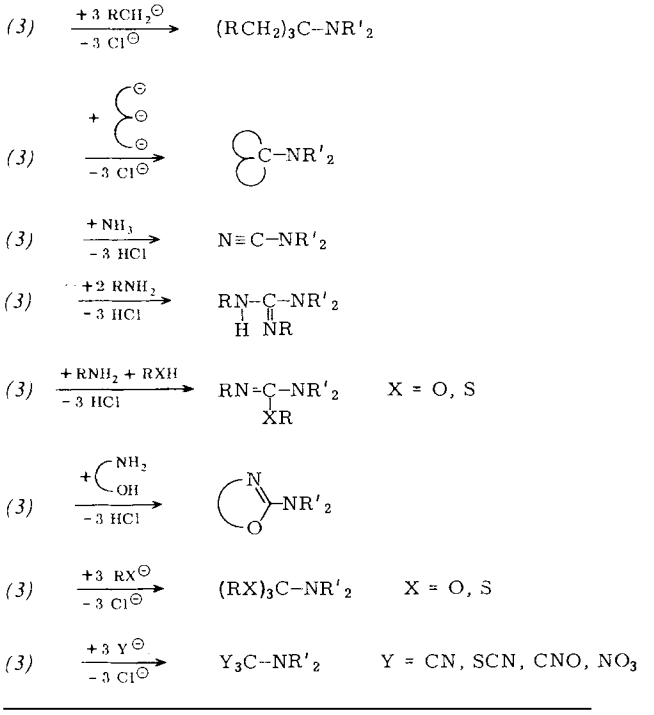
Monosubstitutions with C—X linkage



Disubstitutions



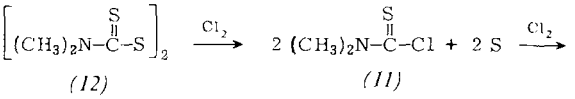
Trisubstitutions



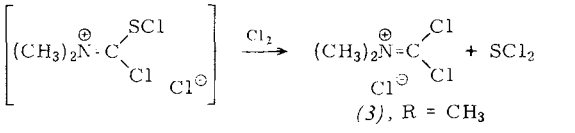
enammonium salts, whose investigation is due in particular to *Arnold* and to *Bredereck*'s school[11], the main contribution of which was the activation of the amides by salt formation. Our own earlier investigations on amide chlorides, α-chloroalkenylamines[12], and alkynylamines[9a], which, particularly with regard to the amide chlorides, was based on work by *Eilingsfeld*, *Weidinger*, and *Seefelder*[13], have helped to acquire the data now available.

2. Synthesis and Characterization of the Dichloromethylenammonium Salts[19, 21a]

The simplest and at present the best synthesis of *N*-dichloromethylene-*N*,*N*-dimethylammonium chloride *(3)*, R = CH_3, which is now commercially available[14], is the chlorination of *N*,*N*-dimethylthiocarbamoyl chloride *(11)* or of the corresponding dithiuram *(12)*[3, 10, 15–17].

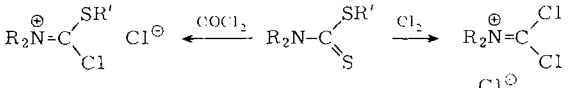


(12) *(11)*



(3), R = CH_3

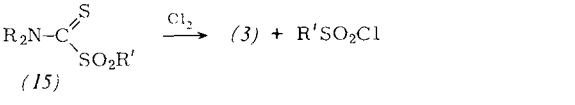
It is well known that *N*,*N*-disubstituted dithiocarbamic esters *(13)* give the salts *(14)* with phosgene, thionyl chloride, or phosphorus pentachloride[18].



(14) *(13)* *(3)*

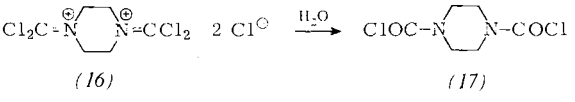
We have found that the readily obtainable dithiocarbamates *(13)* react with chlorine to give *(3)* in very good yields[19].

C-Sulfonylthioformamides *(15)* also give *(3)* on chlorination[20].



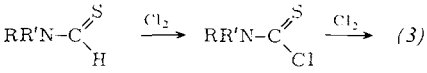
(15)

The first bis(dichloromethylenammonium) salt *(16)* is now also known[19]. Its hydrolysis yields *N*,*N'*-bis(chlorocarbonyl)piperazine *(17)*.



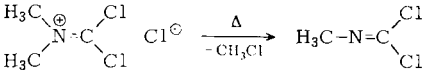
(16) *(17)*

A chemically more elegant route is the chlorination of thioformamides to dichloromethylenammonium salts; the intermediate thiocarbamoyl chlorides need not be isolated[16a]. This shows particularly clearly the relationship with the Vilsmeier and Arnold reagents, which are formed from formamides.



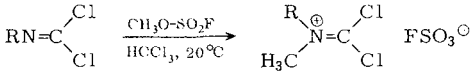
(3)

There is also a close synthetic relationship with the phosgenimines, which have been investigated in particular by *Kühle*[2], and which *Holtschmidt et al.*[15, 21b] have made available by high-temperature chlorination. The phosgenimines are formed by thermal decomposition of *(3)* above 100 °C[19, 21a].

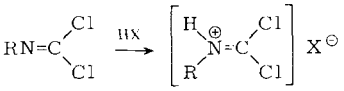


(3), R = CH_3

This reaction can be reversed if methyl fluorosulfates are used for the alkylation of phosgenimines[19]. Less active alkylating agents such as dimethyl sulfate are unsuccessful.

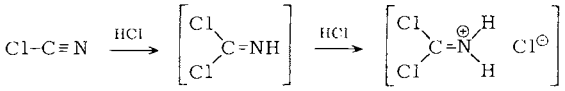


An observation of synthetic interest is that the phosgenimines also form intermediate or acid-isolable dichloromethylenammonium salts *(18)* with a hydrogen atom and an alkyl group on the nitrogen.



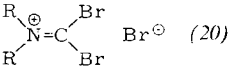
(18)

The simplest dichloromethylenammonium salt *(19)*, with only hydrogen on the nitrogen apart from the dichloromethylene group, is apparently formed as an intermediate in the reaction of cyanogen chloride with hydrogen chloride[22].



(19)

This provides above all dichloromethylenammonium salts that can be converted into primary, secondary, or tertiary amines. The trifluoromethylamines *(21)*[16b, 23] and the as yet unknown mixed chlorofluoromethylenammonium salts will also be of interest, whereas the dibromomethylenammonium salts *(20)*, unlike the apparently unstable iodine derivatives, are obtainable but are found to be much less reactive, probably on steric grounds.



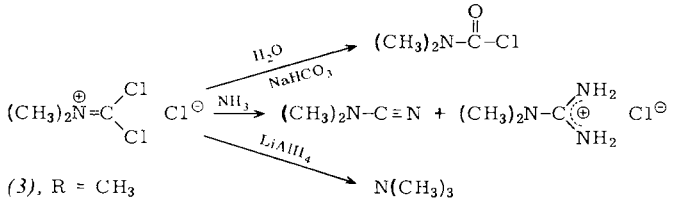
(20)

The salt nature of the dichloromethylenammonium compounds *(3)* is manifested physically in the weak solubility of the lower members of the series in apolar solvents. However, the *N,N*-diethyl derivative can already be recrystallized from dichloromethane or chloroform. Unlike the trifluoromethylamines *(21)*, which are also readily obtainable from *(3)* by reaction with HF or KF[23e], dissolve

$$(3) \xrightarrow[-3\ HCl]{3\ HF/KF} R_2N{-}CF_3 \quad (21)$$

in most solvents, and can be distilled, the dichloromethylenammonium salts show no evidence of the presence of a covalent trichloromethylamine structure. The NMR spectrum shows only one type of compound, *i.e.* that with the ammonium salt structure. In deuterionitromethane, which reacts only slowly with *(3)*, $R = CH_3$, at room temperature[24][*], a sharp singlet is observed at $\tau = 4.07$ ppm. In paraffin suspension, the stretching vibration of the methylenammonium grouping is found at 1625 cm^{-1}.

Chemical evidence of the ammonium salt structure is provided not only by thermolysis but also by hydrolysis, which, in the presence of sodium hydrogen carbonate, can be stopped at the carbamoyl chloride stage or continued to the dialkylammonium chloride, HCl, and CO_2. Reaction of *(3)*, $R = CH_3$, with ammonia leads by "triple condensation" to dimethylcyanamide as well as *N,N*-dimethylguanidinium chloride, and nucleophilic substitution of all three chlorine atoms by hydrogen can be achieved



[*] From monosubstituted nitromethane derivatives, nitriles are formed as end products. Cf. *J. Skramstad*, Acta Chim. Scand. *24*, 3424 (1970).

Dichloromethylenammonium salts and methods for their synthesis are shown in Table 2.

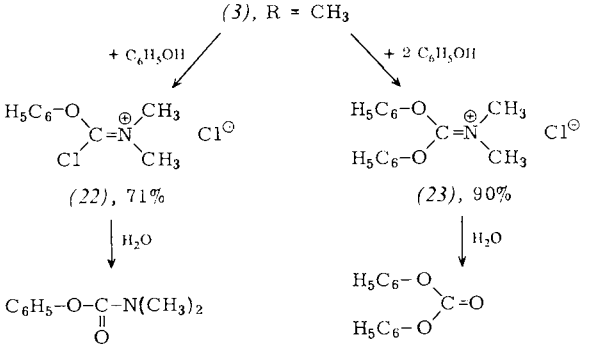
Table 2. Known dichloromethylenammonium salts $R^1R^2\overset{\oplus}{N}{=}CCl_2\ X^{\ominus}$ *(3)* and methods for their synthesis. A: from thiocarbamoyl chlorides, B: from dithiurams, C: from isocyanide dichlorides and methyl fluorosulfate, D: from *(3)*, X = Cl, and $SbCl_5$, E: from isocyanide dichlorides and fluorosulfuric acid, F: from dithiocarbamates, G: from thioformamides, H: from *C*-sulfonylthioformamides.

R^1	R^2	X	Methods	Yield [%]	M.p. [°C]	IR [cm^{-1}]	Ref.
CH_3	CH_3	Cl	A, B, F, G, H	75–90	190	1625	[17, 20, 21a]
CH_3	CH_3	$SbCl_6$	D	95	285–287	–	[17]
C_2H_5	C_2H_5	Cl	A, B	76.82	130	1609	[3, 19]
$(CH_3)_2CH$	$(CH_3)_2CH$	Cl	B	60	207–208	1590	[19]
	$-(CH_2)_4-$	Cl	B	86	120	1605	[19]
	$-(CH_2)_5-$	Cl	B	70	125	1600	[19]
	$-(CH_2)_2-O-(CH_2)_2-$	Cl	A, B	82.54	110	1625	[19]
CH_3	C_6H_5	Cl	B, G	53	–	1600	[19]
CH_3	C_6H_5	FSO_3	C	80	91	–	[19]
CH_3	CH_3	FSO_3	C	95	221	–	[19]
H	C_6H_5	FSO_3	E	96	90–92	–	[19]
CH_3	p-ClC_6H_4	Cl	A	90	111–113	1603	[23a]
CH_3	p-FC_6H_4	Cl	A	91	105–110	–	[23a]
CH_3	p-BrC_6H_4	Cl	A	94	115–116	–	[23a]
CH_3	cyclohexyl	Cl	A	70	151	–	[19, 33]
CH_3	benzyl	Cl	A	70	85	1610	[19, 25]
$-(CH_2)_2-N(CH_3)-(CH_2)_2-$		Cl	F	82	185	–	[19]

3. Reactions of Dichloromethylenammonium Salts with Hydroxy and Amino Functions

3.1. Reactions with Phenols, Alcohols, and Glycols

Phenol[26] reacts smoothly with dichloromethylenammonium salts at room temperature to form the monosubstitution product *(22)*, while heating for 30 minutes under reflux in methylene chloride with a further equivalent of phenol results in disubstitution to form the diphenoxymethylenammonium salts *(23)*, which are stable to excess phenol.

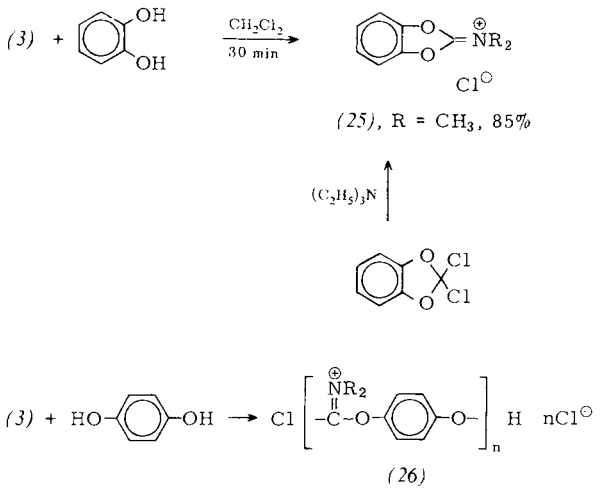


$$(23) \xrightarrow[-CH_3Cl]{140\,^{\circ}C} \begin{matrix} H_5C_6{-}O \\ H_5C_6{-}O \end{matrix}\!\!>\!C{=}N{-}CH_3 \quad (24),\ 91\%$$

They hydrolyze readily to give the diphenyl carbonates, which have been known for some time, and pyrolysis with loss of chloromethane leads in good yields to the iminocarbonates *(24)*.

Thiophenol gives the thio derivatives of *(22)* and *(23)* in yields of 97 and 99% respectively[27].

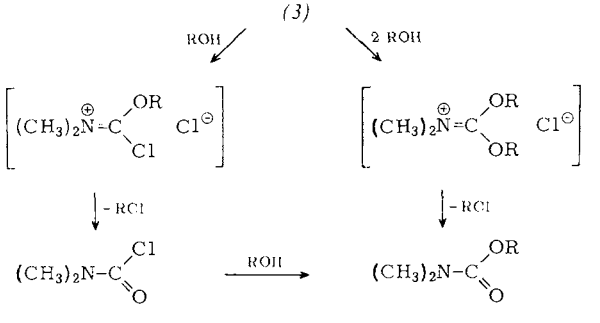
Resorcinol and hydroquinone also react smoothly with *(3)*, R = CH_3, the products being a cyclic [*(25)*] and a polymeric ammonium compound [*(26)*] respectively.



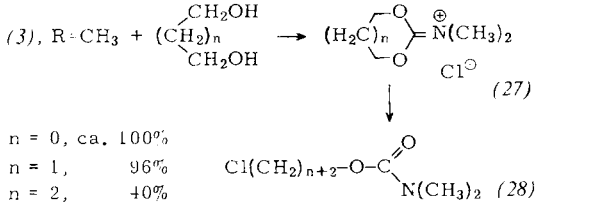
(25), R = C_2H_5, was synthesized earlier from 2,2-dichlorobenzo-1,3-dioxole and triethylamine[28].

In this reaction, *(3)* behaves differently from the methylenammonium and chloromethylenammonium salts, which mostly react with *C*-substitution instead of with *O*-substitution[6c, 29]. *(3)* thus condenses in a similar manner to phosgene.

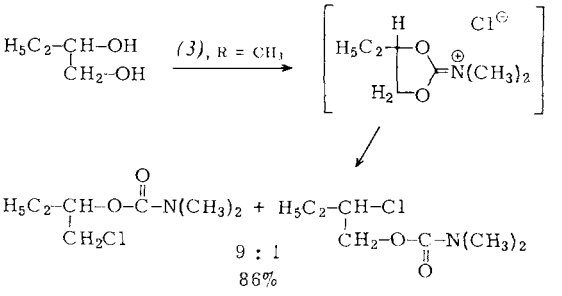
Alcohols react with *(3) via* the mono- or dialkoxymethylenammonium salts to form alkyl chlorides and carbamoyl chlorides and/or carbamates.



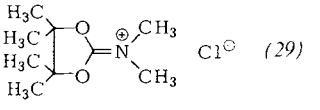
Whereas more detailed investigation of the mechanism of this reaction is still necessary, the study of the reactions of *(3)* with glycols has come to a temporary conclusion. It was found that 1,2-, 1,3-, and even 1,4-diols give ω-chloroalkyl *N,N*-dialkylcarbamates *(28)* stereospecifically and in high yields[30].



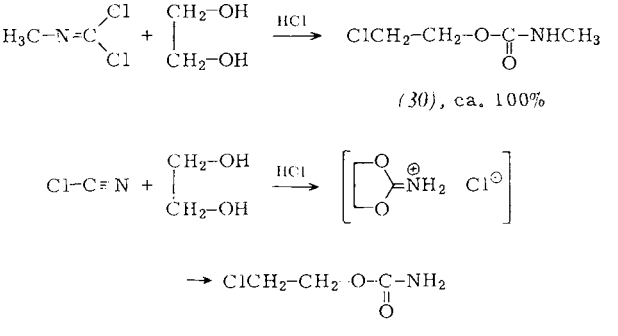
Unsymmetrical glycols give preferentially the derivatives in which the chlorine has substituted the sterically less hindered hydroxyl group[30].



As is shown by the smooth formation of *trans*-chlorocyclohexyl carbamate from *cis*-1,2-cyclohexanediol, the cyclic ammonium salts *(27)* are formed as intermediates by an S_N2 mechanism, and these undergo ring cleavage by nucleophilic substitution with the chloride ion. A similar conclusion is indicated by the observation that the reaction of *(3)* with sterically hindered diols stops at the stage of cyclic compounds of this type. Thus the ammonium salt *(29)* formed from pinacol does not undergo ring cleavage even when heated[30].

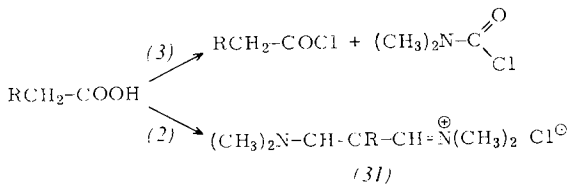


It is interesting to note that dichloromethylenamines react even at room temperature with glycols in the presence of HCl (apparently *via* the ammonium salts) to form ω-chloroalkyl carbamates *(30)* with secondary amide nitrogen[30]. The corresponding reaction of cyanogen chloride was already known[22a].



3.2. Reactions with Carboxylic Acids

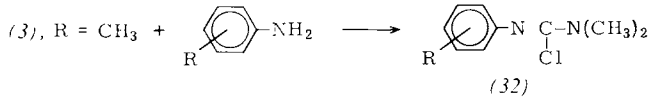
Carboxylic acids are converted into the acyl chlorides by *(3)* under very mild conditions without further condensation with methylene groups in the α position[21a]. The dichloromethylenammonium salts differ in this respect from Vilsmeier and Arnold reagents *(2)*, which are converted by condensation and decarboxylation into cyanines *(31)*[31]. This reaction probably proceeds *via* ketene intermediates[32].



(31)

3.3. Reactions with Amines

The condensation of (3), R = CH_3, with ammonia to form dimethylcyanamide was mentioned in Section 2. Reaction with primary amines leads smoothly to the expected chloroformamidines (32) or their hydrochlorides. It is interesting to note that even such weakly basic amines as sulfonamides and 2,4-dinitroaniline react smoothly. The results are listed in Table 3.



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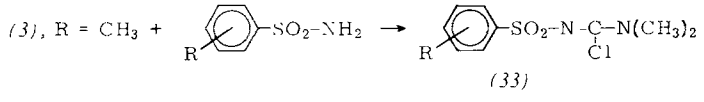
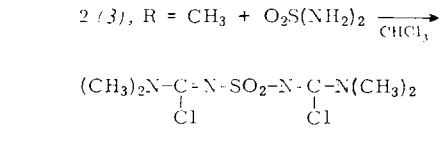


(33)

Table 3. Chloroformamidines (32) and N^2-sulfonylchloroformamidines (33) prepared from dichloromethylenedimethylammonium chloride (3), R = CH_3.

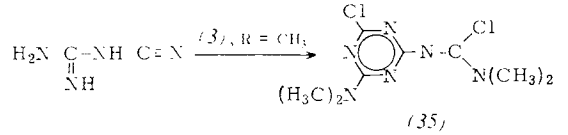
	Yield [%]	B.p. [°C/torr] M.p. [°C]	Ref.
(32), R = H	67	81/0.5	[21a]
(32), R = p-$CO_2C_2H_5$	96	65	[26]
(32), R = p-NO_2	80	102	[26]
(32), R = 2,4-$(NO_2)_2$	87	97	[26]
(33), R = H	94	65—66	[21a]
(33), R = p-CH_3	76	152—154	[17, 33]
(33), R = p-Cl	85	143	[17, 33]

Sulfamide gives the bis(chloroformamidine) (34)[33], m.p. 127—128 °C.



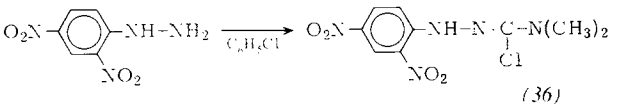
(34), 97%

1-Cyanoguanidine gives the 1,3,5-triazine derivative (35), m.p. 105—107 °C, in a yield of 81%[21a].



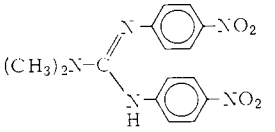
(35)

2,4-Dinitrophenylhydrazine reacts with (3), R = CH_3, to form the hydrazone (36) of *N*,*N*-dimethylcarbamoyl chloride, 87% yield, m.p. 198 °C (dec.)[21a].



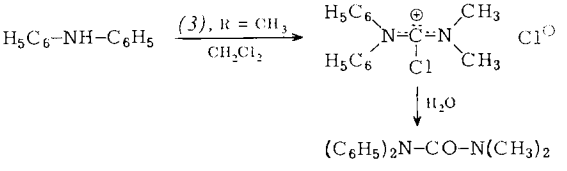
(36)

Guanidines of the type (37) have been synthesized from (3), R = CH_3, and 2 moles of *p*-nitroaniline[17].

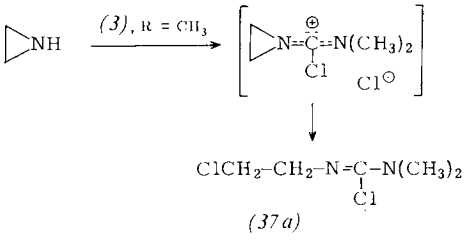


(37), 58%

Secondary amines react with (3) to form urea dichlorides. Even diphenylamine reacts smoothly at 40 °C with practically quantitative yields[21a]. Dimethyl-*N'*,*N'*-diphenylurea was obtained by hydrolysis, 83% yield, m.p. 65 °C.



Ethylenimine (aziridine) gives (37a) as a rearrangement product[27].



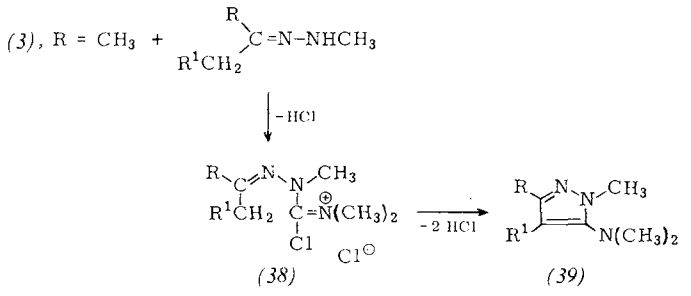
(37a)

Unlike phosgene, (3) reacts with tertiary amines simply with complex formation in most cases and without degradation. For this reason, *e.g.* triethylamine can be used as a basic catalyst in CH condensation reactions, which are discussed in Section 6.

4. Heterocyclizations with Dichloromethylenammonium Salts

4.1. Reactions with Hydrazones, Phenylhydrazines, Hydrazides, and Amidrazones

Hydrazones react with (3), R = CH_3, to form the 1,3,4-trisubstituted 5-dimethylaminopyrazoles (39). The semicarbazone dichlorides (38) can be intercepted as intermediates. When heated in chloroform solution or in the absence of solvent they cyclize[34] (Table 4).

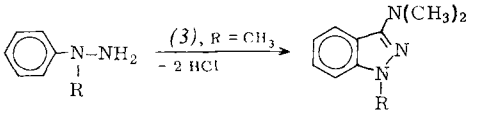


(38) (39)

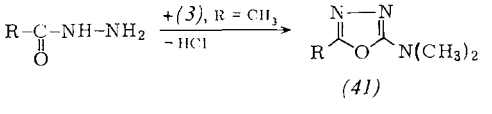
Table 4. 5-Dimethylamino-1-methylpyrazoles *(39)* prepared from hydrazones and *(1)*.

R	R^1	Yield [%]
C_2H_5	CH_3	81
CH_3	C_2H_5	70
C_6H_5	H	24
—$(CH_2)_3$—		—
—$(CH_2)_4$—		81
—$(CH_2)_5$—		84
—$(CH_2)_6$—		84
—*o*-C_6H_4—CH_2CH_2—		76

The dialkylaminoindazoles *(40)* are formed similarly from phenylhydrazines[35]; hydrazides react with *(3)*, R = CH_3, to form 1,3,4-oxadiazoles *(41)* (Table 5). The reaction of amidrazones with *(3)*, R = CH_3, yields the 1,2,4-triazole derivatives *(42)*, of which two examples [*(42a)* and *(42b)*] are given, while heterocyclization to form five-membered rings occurs with *o*-phenylene derivatives (diamines, diols, hydroxyamines)[35,18a].



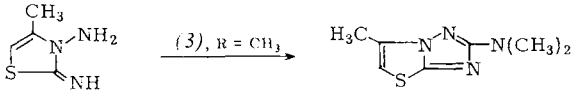
(40); R = C_6H_5, 83%



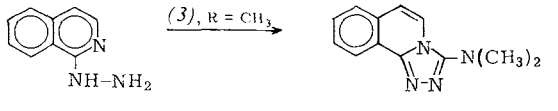
(41)

Table 5. 2-Dimethylamino-1,3,4-oxadiazoles *(41)* prepared from hydrazides and *(1)*.

R	Yield [%]	M.p. [°C] b.p. [°C/torr]
CH_3	90	100/0.1
$CH_2C_6H_5$	93	75–76
4-pyridyl	95	118–120



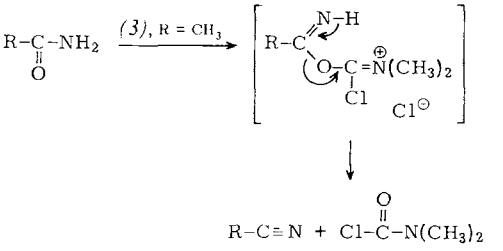
(42a), 95%



(42b), 89%

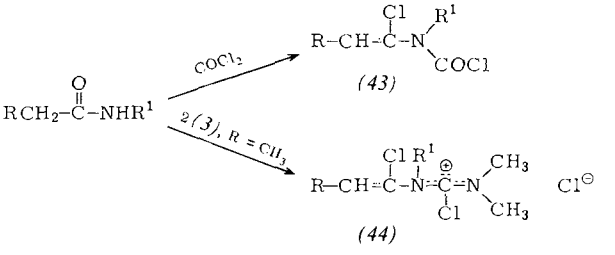
5. Reactions of Dichloromethylenammonium Salts with Primary and Secondary Acetamides

Primary amides react smoothly with *(3)*, R = CH_3, to form nitriles. Dichloromethylenammonium salts thus act merely as dehydrating agents here.



Secondary acetamides having a methylene group α to the carbonyl group react with *(3)* with *N*-acylation and also with replacement of the amide oxygen by chlorine.

Comparison of this reaction, which leads to *N*-(1-chloro-1-alkenyl)chloroformamidinium salts *(44)*[36] (Table 6), with the reaction of phosgene[37] again shows the close relationship between the two reagents.



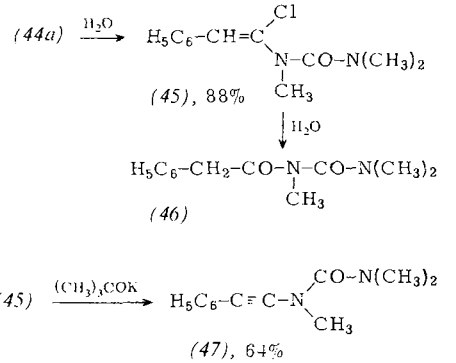
(43)

(44)

Table 6. *N*-(1-Chloro-1-alkenyl)-*N'*,*N'*-dimethylchloroformamidinium chlorides *(44)* prepared from N secondary acetamides and *(1)*.

(44)	R	R^1	Yield [%]	M.p. [°C]
(a)	C_6H_5	CH_3	97	82–85
(b)	Cl	CH_3	85	154
(c)	—$(CH_2)_4$—		86	liq.
(d)	H	CH_3	90	liq.

Hydrolysis of *(44a)* leads first to the *N*-(α-chlorostyryl)-urea *(45)* and then to the *N*-acylurea *(46)* (71% yield, b.p. 135 °C/0.2 torr)[36].

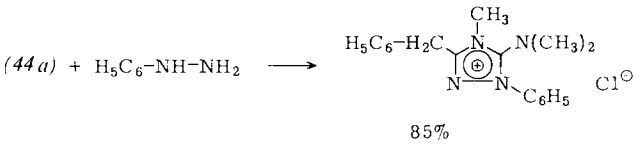


(46)

(47), 64%

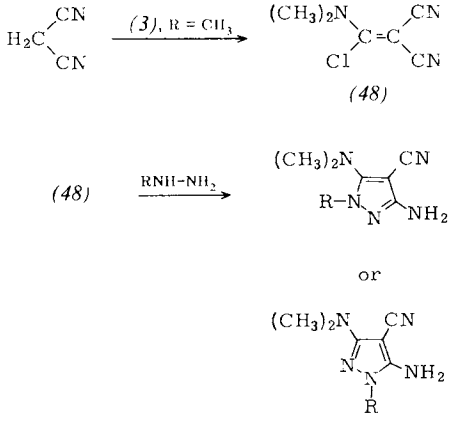
Dehydrochlorination both of *(45)* and of *(43)* leads readily to derivatives of the previously practically uninvestigated alkynylamides, *e.g. (47)*[36,38,39].

(43) and *(44)* can also be used as 1,3-di-electrophiles for heterocyclization reactions[38,59].

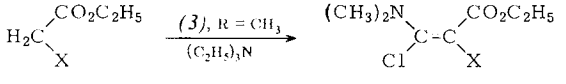


6. CC Bonds Between Activated Methylene Groups and Dichloromethylenammonium Salts

Of all the malonic acid derivatives, malodinitrile reacts most readily with *(3)*[21a]. Heating under reflux in chloroform for 30 minutes gives 2-chloro-2-(dimethylamino)ethylene-1,1-dicarbonitrile *(48)* (b.p. 180 °C/0.5 torr) in 77% yield[21a,40b]. The product promises to become a useful heterocyclization reagent, as is shown *e.g.* by the reaction with phenylhydrazine[40a].



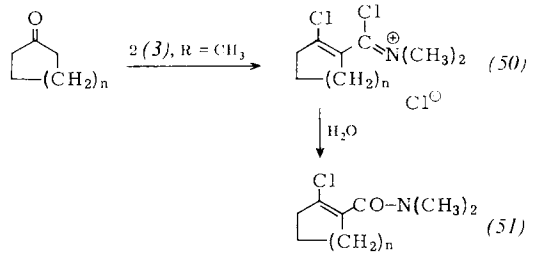
Cyanoacetic ester reacts only slowly with *(3)* without the addition of triethylamine, while malonic diester requires the base for condensation in any case. In the presence of triethylamine, both give good yields of the 2-amino-2-chloroethylene derivatives *(49)*[21a,40,42].

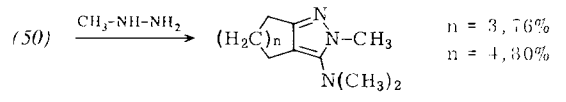


(49a), X = $CO_2C_2H_5$, 70%
(49b), X = CN, 85%

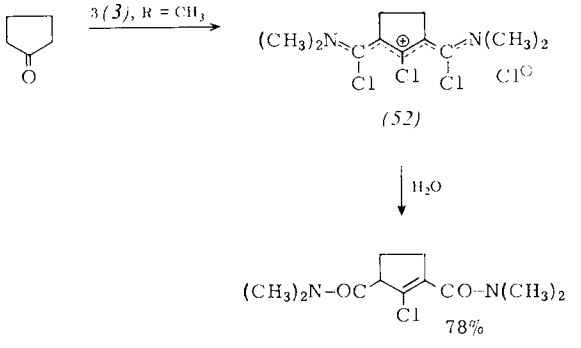
7. Condensation Reactions of Dichloromethylenammonium Salts with Ketones

Whereas phosgene usually reacts with ketones only if the latter have first been converted into the enolates[41], dichloromethylenammonium salts in many cases condense extremely readily with ketones. Thus the higher cycloalkanones give almost quantitative yields of the β-chloroacrylamide derivatives *(50)*[42], which can be readily hydrolyzed to the amides *(51)* and can be used as 1,3-di-electrophiles for numerous heterocyclizations[43] [*(50)*, $n=2$, 98%; $n=3$, 88%; $n=4$, 90%; *(51)*, $n=2$, 72%, b.p. 99 to 102 C/0.6 torr; $n=3$, 87%, b.p. 130 C/0.6 torr; $n=4$, 75%, b.p. 140 C/0.6 torr].

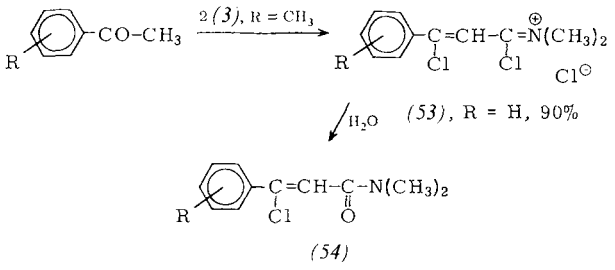




Cyclopentanone reacts with three moles of *(3)* to give a red pentamethinecyanine *(52)*, $\lambda_{max}=536$ nm; cyclobutanone (according to preliminary experiments) behaves similarly[42].

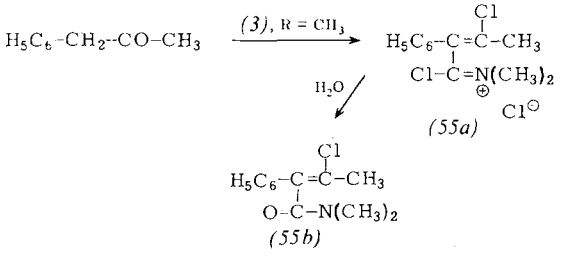


Comparison of the Vilsmeier-Haack and Arnold reagents *(2)*[44,45] with the dichloromethylenammonium salts *(3)* again shows the greater reactivity of the compounds *(2)*, which always react with dicondensation or polycondensation. Steric and electronic factors evidently have a combined deactivating effect in the dichloromethylenammonium salts. The strong dependence of the reaction on steric effects is also seen in the behavior of the dichloromethylenammonium salts toward acetophenone and propiophenone. Only acetophenone reacts smoothly to form the *N,N*-dimethylcinnamamide derivative *(53)*[21a], whereas propiophenone condenses with the Vilsmeier reagents[46] but not with dichloromethylenammonium salts. Hydrolysis of *(53)* leads to the β-chlorocinnamamide derivative *(54)*, whose dehydrochlorination readily yields the phenylpropiolamide derivative. The ring-substituted derivatives of acetophenone behave in the same way as acetophenone itself toward *(3)*[21a]. Pinacolone and even isopropyl methyl ketone are apparently too strongly hindered and do not react with *(3)*. [*(54a)*, R=H, 70%, b.p. 165 °C/0.2 torr; *(54b)*, R=*p*-Cl, m.p. 65—68 °C; *(54c)*, R=*p*-NO_2, m.p. 108—111 °C; *(54d)*, R=*m*-NO_2, m.p. 78 °C].

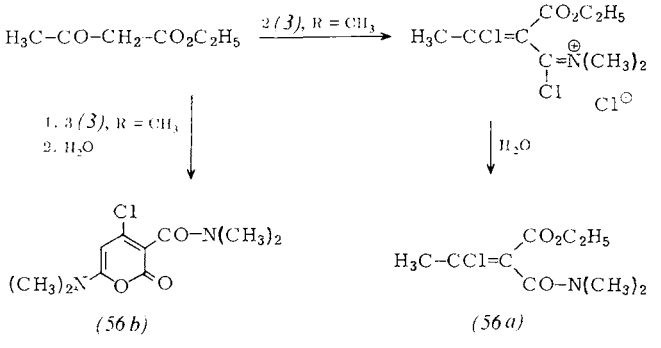


(54)

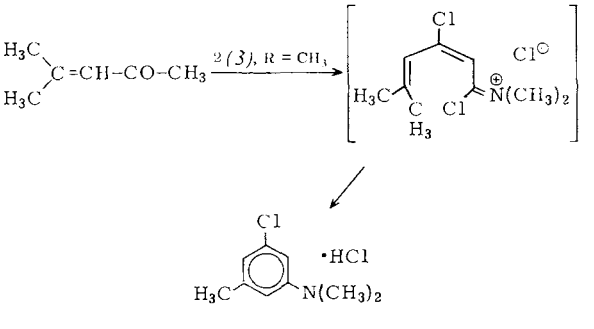
Benzyl methyl ketone reacts with *(3)*, R = CH_3, to form *(55a)*, which gives the methylacrylamide *(55b)*, b.p. 138 C/0.15 torr, in 75% yield on hydrolysis[42].



Reaction of three moles of *(3)* with acetoacetate gives not only the isolable monocondensation product *(56a)* (27% yield, b.p. 100 C/0.2 torr) but also the α-pyrone derivative *(56b)* (20% yield, m.p. 150—151 C, λ_{max} = 370 nm, ε = 33400).



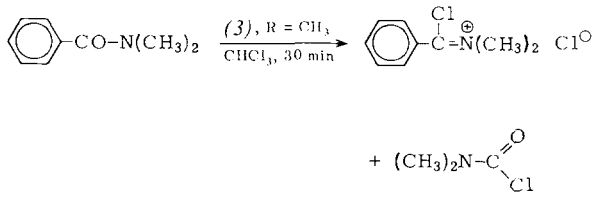
Mesityl oxide also reacts with double condensation and ring closure to form a benzene derivative [m.p. 204 C (dec.)][21a].



In view of these reactions with ketones, it is surprising that the aldehydes investigated so far do not react with dichloromethylenammonium salts with formation of a new CC bond, but undergo substitution of the aldehyde oxygen by chlorine. To explain this difference in behavior we assume that it is due to differences in the tendency to enolize and/or to steric effects.

8. Reactions of Dichloromethylenammonium Salts with Tertiary Amides

Tertiary amides have a nucleophilic oxygen atom, which is replaced by chlorine on reaction with *(3)*. Thus reaction of *N*,*N*-dimethylbenzamide with *(3)* leads readily to the amide chloride (yield 90%). Phosgene also reacts, but much more slowly[47]. The amide chloride formation merits more detailed investigation in connection with the substitution of oxygen functions by chlorine (alcohols, glycols, aldehydes, epoxides, and carboxylic acids).



So far we have studied mainly tertiary acetamides with an α-CH_2 group. Their reactions with phosgene were known to us from earlier work[12]. The amide chloride formation is followed in some cases by condensation with phosgene, though usually only in moderate yields. On the other hand, dichloromethylenammonium salts react smoothly to form the long-sought dichlorotrimethinium salts *(57)* (Table 7), which may be regarded as bis(amide chlorides) of malonyldiamides[21a, 49, 50]. Comparison with malonic acid derivatives also shows the possibility of using the compounds *(57)*, which are now readily obtainable, for the synthesis of bis(dialkylamino) heterocycles (cf. Sec-

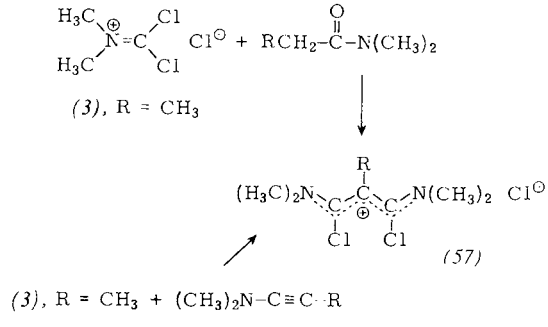
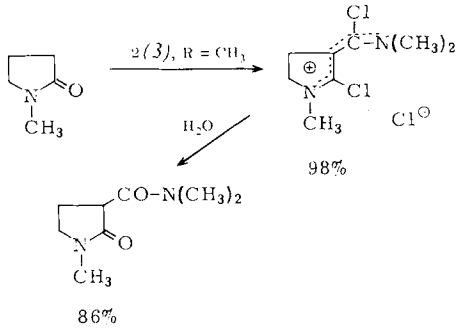


Table 7. Dichlorotrimethinium salts *(57)* prepared from N tertiary acetamides and *(1)*.

R	Yield [%]	UV (CH_2Cl_2) λ_{max} [nm]	Ref.
H	91	346	[49]
C_2H_5	88	388	[49]
C_6H_5	90	397, 278	[49]
Cl	88	410	[49]
CH_3	90	—	[21a]
F	71	—	[21a]
$CH(CH_3)_2$	75	—	[21a]
OCH_3	95	406	[50]
OC_2H_5	98	409	[50]
$OCH(CH_3)_2$	92	407	[50]
OC_6H_5	99	406	[50]

tion 9). The compounds *(57)* are also obtainable in practically quantitative yield by addition of *(3)* to alkynylamines[48].

As was to be expected, cyclic tertiary amides also couple with *(3)*[21a].



These cyanines are characterized chemically by hydrolysis, thiolysis, and aminolysis to derivatives of malonamides *(58)*, malonthioamides *(59)*, and malonamidines *(60)*[49]; these reactions are the simplest syntheses of these compounds known at present (Table 8).

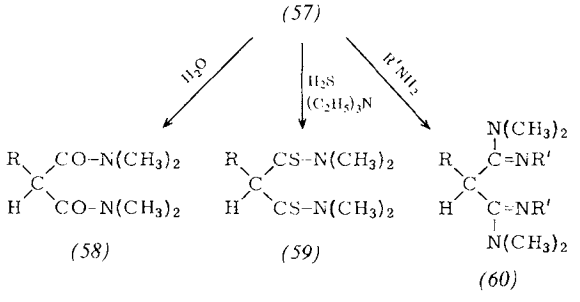
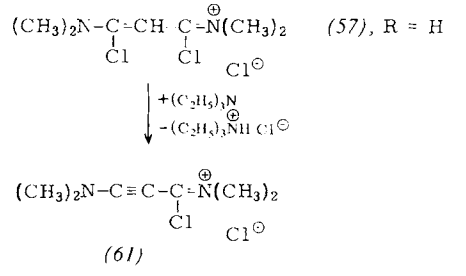
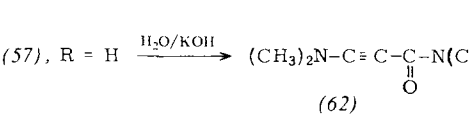


Table 8. Malonamides *(58)*, malonthioamides *(59)*, and malonamidines *(60)* prepared from *(57)*.

Cpd.	R	Yield [%]	M.p. [°C] b.p. [°C/torr]
(58)	C_2H_5	75	76
(58)	Cl	73	92
(58)	C_6H_5	78	149
(59)	H	70	107
(59)	C_2H_5	83	178
(59)	C_6H_5	55	193
(60)	H, R′ = CH_3	61	75/0.5



(57), R = H

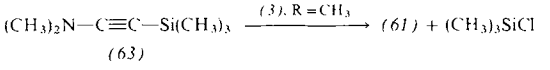


(61)

(62)

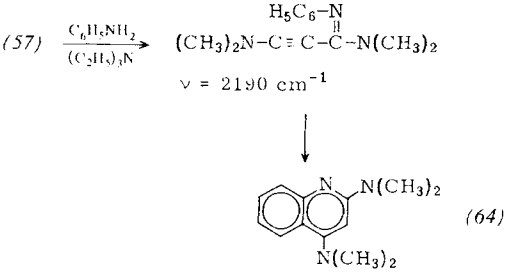
The 3-aminopropynylenammonium salt *(61)* [IR: ν = 2212, 2243 cm^{-1}] is obtainable from *(57)*, R = H, and triethylamine[21a]; reaction with aqueous alkali yields 3-dimethylaminopropiolamide *(62)*[51, 21a].

The compound *(61)* is also readily obtainable from the silylalkynylamine[52] *(63)* and *(3)*[53a], but trimethylsilyl chloride is formed as a by-product in this case.



(63)

With alkaline hydrogen sulfide, the malondithioamide *(59)* is obtained directly from *(57)*. The behavior of aniline is interesting, as it reacts readily with *(57)* to form 2,4-bis-(dimethylamino)quinoline *(64)*[53b–53d].



(64)

Secondary amines react with *(57)* to form the tetrakis(dialkylamino)allenium salts *(65)*. These are stable to hydrolysis and can be easily isolated as perchlorates or chlorides. *(65)* may be regarded as salts of tetrakis(dialkylamino)allenes *(66)*. The latter are in fact obtained from *(65)* by treatment with butyllithium or sodamide. The compounds *(66)* merit investigation as electron-rich allenes[21a, 54] (Table 9).

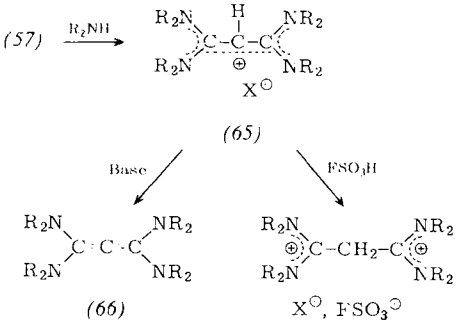
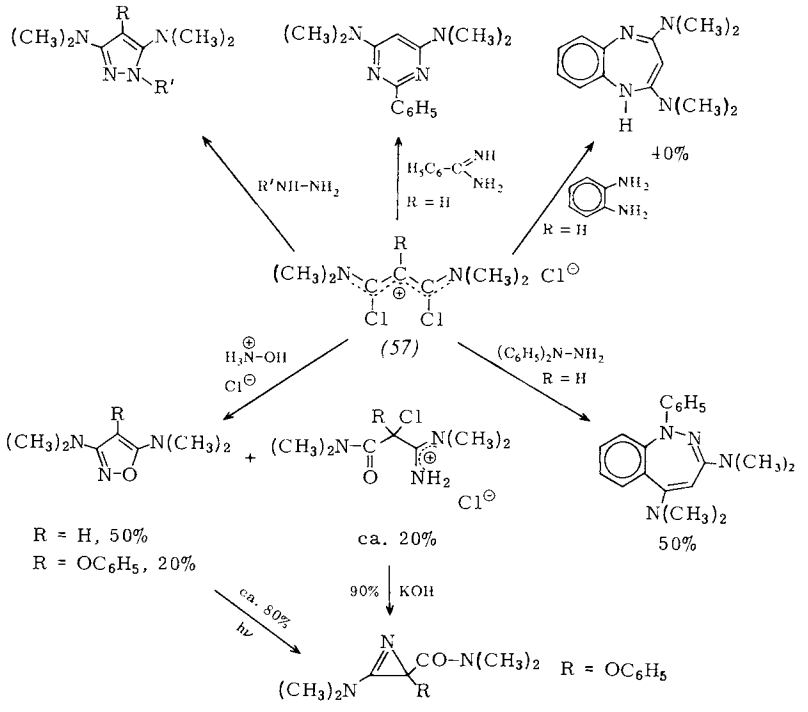


Table 9. Allenium salts *(65)* and allenes *(66)* prepared from *(1)* *via* *(57)*.

Cpd.	R	X	Yield [%]	M.p. [°C] B.p. [°C/torr]
(65a)	CH_3	ClO_4	85	174
(65b)	C_2H_5	Cl	91	liq.
(66)	C_2H_5		70	120/0.5

9. Heterocyclizations with Dichlorotrimethinium Salts *(57)*

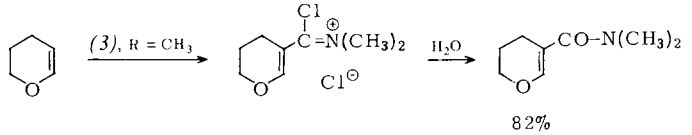
A number of heterocyclizations have been carried out with *(57)* (cf. Section 8)[58]. The compound may be

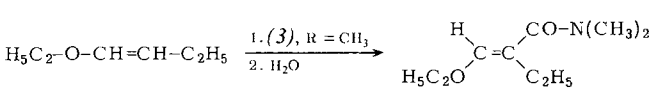


regarded as a vinylogous dichloromethylenammonium salt, like the condensation products of ketones and *(3)*, and it may therefore be expected that the cyclizations that are possible with *(3)* should also be possible with *(57)*, though rings containing two additional atoms would result. The scheme above shows the formation of five-membered and seven-membered heterocycles. We merely mention that in an attempt to synthesize an isoxazole, an azirine was also formed by free-radical side reactions[55].

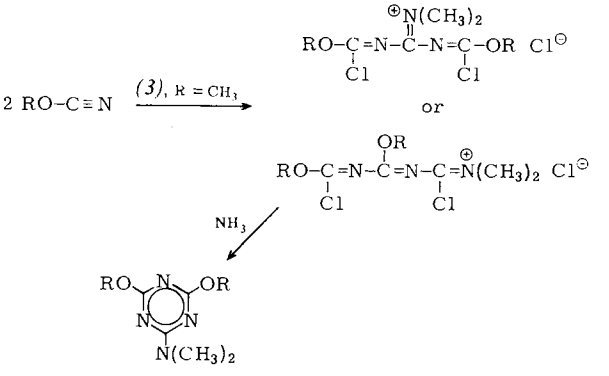
10. Addition of Dichloromethylenammonium Salts to Multiple Bonds

Electron-rich double and triple bonds undergo addition with *(3)*, and in the presence of β-hydrogen, this may be followed by elimination of HCl. *(3)* adds to vinyl ethers; subsequent hydrolysis leads to unsaturated carboxamides[21a].



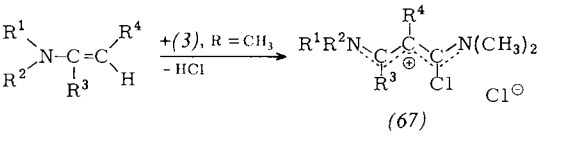


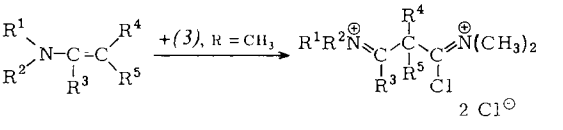
The addition of *(3)* to alkynylamines was mentioned in Section 8. Similar behavior is observed with electron-rich nitriles such as alkylcyanamides (see Section 12) and cyanates. The directiospecificity in the diaddition of cyanates has not been investigated in detail[56].



11. Reactions of Dichloromethylenammonium Salts with Alkenylamines

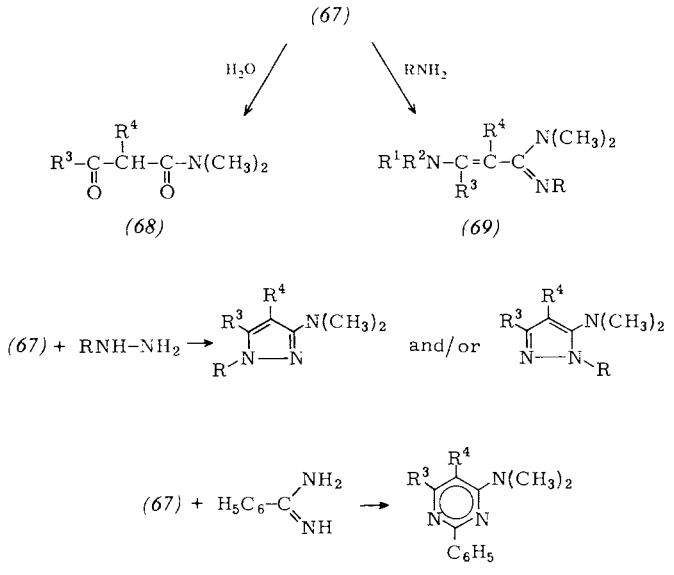
As electrophilic reagents, dichloromethylenammonium salts add readily to alkenylamines in the same way as phosgene[56].





The resulting trimethinecyanines *(67)* are useful reagents[57]. Hydrolysis yields tertiary β-keto amides *(68)*, while aminolysis leads to 3-aminoacrylamidines *(69)*.

As di-electrophiles, the compounds *(67)* condense readily with dinucleophiles, *e.g.* hydrazines and amidines.



12. Addition of Dichloromethylenammonium Salts to Cyanamides[48]

This reaction gives azacyanines *(70)* in very good yields (Table 10).

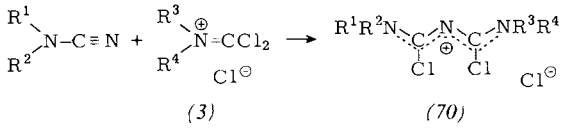
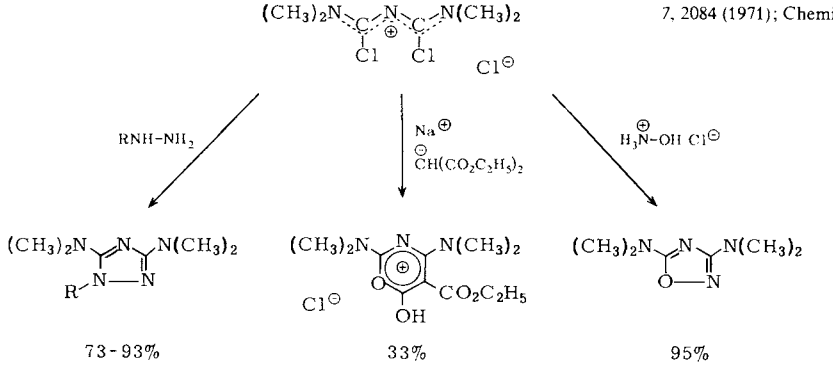


Table 10. Azacyanines *(70)* prepared with *(1)*.

R^1	R^2	R^3	R^4	Yield [%]	λ_{max} [nm]	Ref.
CH_3	CH_3	CH_3	CH_3	93	282	[48]
CH_3	CH_3	CH_3	C_6H_5	93	285	[25]
CH_3	CH_3	CH_3	$CH_2C_6H_5$	96	286	[25]
$CH_2C_6H_5$	CH_3	CH_3	$CH_2C_6H_5$	92	289	[25]

Heterocyclizations similar to those carried out with the trimethinecyanines *(57)* are also possible with the azacyanines, *e.g. (70)*, $R^1=R^2=R^3=R^4=CH_3$[59].



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Syntheses of Seven- and Five-Membered Rings from Allyl Cations

By H. M. R. Hoffmann[*]

The cycloaddition of allyl cations to conjugated dienes offers an efficient and general tool for the construction of seven-membered carbocycles. The silver salt route is highly suitable for generating allyl cations and can be used even in most difficult cases, *i. e.* for elusive and intractable allyl cations such as 2-methylallyl, 2-methoxyallyl, and the parent allyl cation. Cycloadditions to the 2-methoxyallyl cation come very close to the prototype of a 6π,7C reaction, since the carbonyl group introduced into the new ring can either be used for further transformations or be removed altogether. The combination of an allyl cation with π reactants, especially conjugated dienes, is a powerful and strongly convergent synthetic method since it permits one-step assembly, from a C_3 and a C_4 unit, of a cluster of up to four chiral centers in a ring which is larger than six-membered. Allyl cations combine with electron-rich 2π systems to form novel five-membered rings. The nature of the organometallic intermediates has been elucidated in many cases.

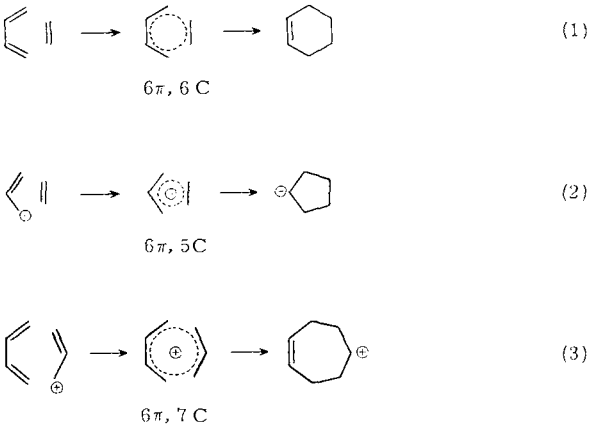
1. Introduction

Of the trilogy of cycloadditions involving 6π electrons (Scheme 1) the Diels-Alder addition [eq. (1)] discovered more than forty years ago, has remained perhaps one of the best known and most useful reactions of organic chemistry[1]. Similarly, since its general conception by *Huisgen* in the late 1950's the 1,3-dipolar addition [eq. (2)] has been firmly established and opened a standard route to a wide range of five-membered heterocycles[2]. Of course, on entropy grounds, both five- and six-membered rings are formed readily, also by various other routes, and indeed are abundant in Nature.

In contrast, seven-membered carbocycles have been much harder to come by and until recently only specialized procedures such as ring contraction and expansion sequences have been employed. While the combination of an allyl cation with a conjugated diene [eq. (3)] had been shown to be feasible, the reaction was considered a curiosity without practical interest and did not attract any general attention.

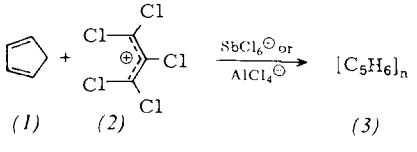
It is worth while to bear in mind that allyl systems as such have held a key position in the history of organic chemistry and, notably in the hands of *Ingold* and *Winstein*, have contributed to the evolution of concepts such as mesomerism, tautomerism, and ion pairs[3]. More recently, the enormous amount of solvolytic work has been complemented by a study of long-lived allyl cations, which were investigated in highly acidic media and also relatively weak acids such as concentrated sulfuric acid[4].

However, it is now clear that neither of the two experimental extremes employed in the past are of much use in synthetic work. Specifically, an allyl cation generated solvolytically appears to be too short-lived and to react preferentially with the solvent, whereas the highly acidic media required for observing carbocations at equilibrium preclude the coexistence of many and potentially more interesting reaction partners[5].



Scheme 1. Cycloadditions involving 6π electrons.

Interestingly, stable allyl cations can cause problems even if they can be handled in solvents which are inert to conjugated dienes. For instance, attempts to combine the long-lived pentachloroallyl cation *(2)*[6] with cyclopentadiene in dichloromethane or liquid sulfur dioxide were not successful and only cyclopentadiene polymer was observed *(3)*[7]. It cannot be entirely ruled out that a seven-membered adduct is formed initially in this reaction, but the probability of obtaining a stable neutral compound in the absence of a suitable anion seems remote.

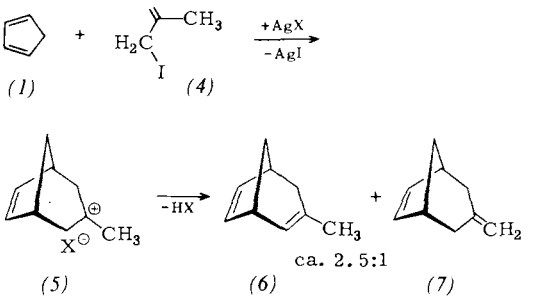


2. The Silver Salt Route to Seven-Membered Rings[8]

In order to couple an allyl cation and a conjugated diene according to eq. (3) a number of new techniques had to be developed. For several reasons the conditions described by us early in 1968[5,8] have remained close to ideal for handling even simple and highly unstable allyl

[*] Dr. H. M. R. Hoffmann
William Ramsay and Ralph Forster Laboratories
University College, London WC1H OAJ (England)

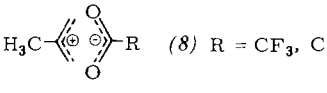
cations which are free from terminal substituents (Scheme 2).



(1) (4) (5) (6) (7)

Scheme 2. Example of the silver salt route. Reaction is carried out in isopentane or benzene at −78 to 0 °C; X = $F_3C—CO_2$ or $Cl_3C—CO_2$ [5, 8].

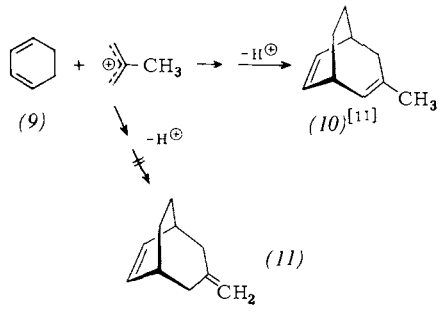
1) In choosing an allylic iodide[5] rather than a bromide or chloride, one takes advantage of the best possible leaving group that can be removed by the electrophilic catalyst. 2) Silver ion removes the iodide ion efficiently and irreversibly[9] and leaves no room for the formation of hydrogen iodide, which would attack both reactants and products. 3) Perhaps most important is the nature of the silver anion, which acts as a co-catalyst in the reaction. In general, the choice of trichloroacetate[5] and trifluoroacetate[10] represents a happy compromise in that these anions are not sufficiently nucleophilic to trap substantial amounts of the intermediate allyl cation, but might actually stabilize it as shown in (8). On the other hand, in the final stage



(8) R = CF_3, CCl_3

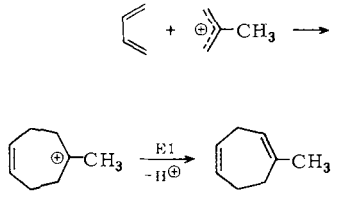
of the reaction the anion can combine with a proton to give a halogenated acetic acid which does not do any significant damage to reactants or products; alternatively the anion forms an ester with the 4-cycloheptenyl cation[*]. 4) A fairly large number of solvents ranging from liquid sulfur dioxide, benzene, diethyl ether, to benzene in CCl_4, and isopentane or even no solvent at all have been used by us. In general it seems desirable that the silver salt be present heterogeneously, since the formation of allyl ester can usually be minimized in that way. The cycloaddition in pentane or isopentane is preparatively perhaps most convenient.

Given these conditions, cyclopentadiene (1) and the 2-methylallyl cation afforded a mixture of the bicyclics (6) and (7) in a ratio of *ca.* 2.5:1. In an analogous experiment with 1,3-cyclohexadiene (9) only 3-methylbicyclo[3.2.2]nona-2,6-diene (10) was formed and none of the isomer (11)[5, 10]. This contrasting distribution of products can be ascribed to the greater flexibility of the ethano bridged 1,4-cycloheptadiene (10) *vis-à-vis* the methano analog (6). In the latter compound the newly formed double bond can be accommodated by the seven-membered ring only at the expense of additional strain and formation of the isomer (7) with an exocyclic double bond competes.



(9) (10)[11] (11)

That the final proton loss is an E1 reaction, which is subject to Saytzeff control, could be confirmed by the reaction of butadiene with the 2-methylallyl cation, which furnished the thermodynamically more stable trialkylated olefin (12) as the sole cycloadduct[10].

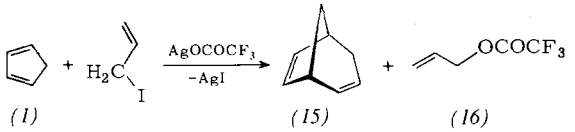


(12)

From a preparative point of view, open-chain dienes such as butadiene, isoprene, and 2,3-dimethylbutadiene present obvious problems. Since the energy level of the cisoid conformer (14) required for a concerted cycloaddition lies at least 2 kcal mol^{-1} above that of the transoid conformer (13) at any given moment the proportion of butadiene molecules available for reaction amounts to *ca.* 4% at ambient temperature, but at −78 °C to less than 0.7%[10]. Hence, a simple allyl cation which lacks the stabilization afforded by terminal substituents has only a poor chance of combining with a cisoid partner below 0 °C and it comes as no surprise that the yields are relatively low (< 10%) in this case[10].

(13) (14)

As expected cycloadditions of the parent allyl cation proved to be extremely difficult. Nonetheless, reaction has been realized, bicyclo[3.2.1]octa-2,6-diene (15) and 2-propenyl trifluoroacetate (16) being formed from simple starting materials in one stage[10].

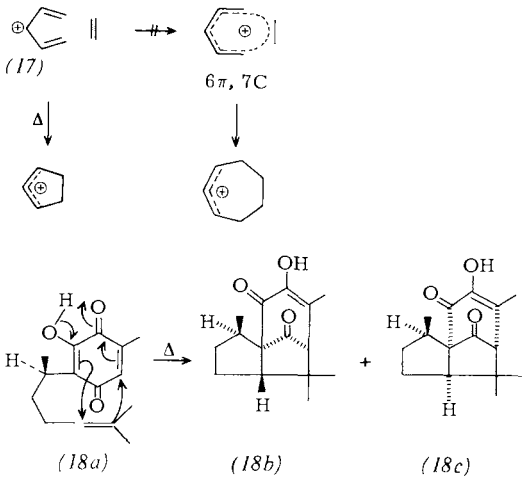


(1) (15) (16)

Parenthetically, it should be mentioned that the combination of a pentadienyl cation (17) and an olefin is frustrated

[*] Since the above was written, the use of silver salts for generating reactive 2π [10a] and 4π components [10b] in other types of cycloaddition has been reported. However, as the reactive intermediates and the products obtained were more stable than ours, the choice of silver counterion is less important and $AgBF_4$ can be employed without apparent difficulty; see also *G. F. P. Kernaghan* and *H. M. R. Hoffmann*, J. Amer. Chem. Soc. 92, 6988 (1971).

by the ease of intramolecular cyclization of the carbocation[4,12]. However, an interesting, and hitherto the only example, which is also of biogenetic interest, is the transformation of the naturally occurring perezone *(18a)* into the isomeric pipitzols *(18b)* and *(18c)* on heating in tetralin[13,14]. Note that conrotatory closure of the 4π,5C system in perezone *(18a)* is unfavorable on steric grounds, whereas no such factors mitigate against the formation of the products *(18b)* and *(18c)*, which belong to the cedrane class of sesquiterpenes.

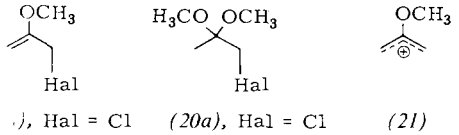


(18a) *(18b)* *(18c)*

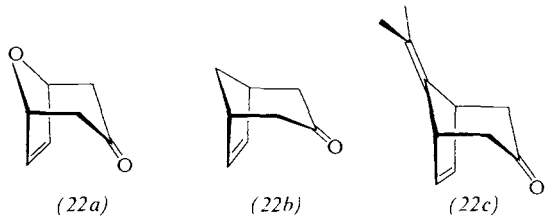
3. The 2-Methoxyallyl System

2-Alkoxyallyl halides represent a simple class of bifunctional compounds which curiously had been unknown until we uncovered two simple and efficient routes to the series of parent halides *(19a)–(19c)*. For example, 2-methoxypropene and *N*-bromosuccinimide give an array of at least five products, but under carefully controlled conditions the desired compound *(19b)* can be isolated in more than 50% yield[15].

The reactivity of the 2-methoxyallyl halides *(19)* relative to that of other allyl halides is of intrinsic interest, even though a solvolytic comparison appears to be ruled out, since the compounds *(19a)—(19c)* are also enol ethers which at least in unbuffered conditions react with all common protic solvents. Thus, on contact with neutral methanol at room temperature the ketals *(20)* were formed almost before one could scan an NMR spectrum. However, it seems clear that the methoxy grouping alters the reactivity pattern considerably. For example, *(19a)* and *(19b)* were less reactive than the corresponding 2-methylallyl halides in typical S_N2 reactions (displacement by iodide ion in acetone[5,15], by carbonylmetal anions, and by sodium alkoxides[16]).



(19a), Hal = Cl *(20a)*, Hal = Cl *(21)*
(19b), Hal = Br *(20b)*, Hal = Br
(19c), Hal = I *(20c)*, Hal = I



(22a) *(22b)* *(22c)*

In an S_N1 like reaction (silver trifluoroacetate, isopentane solvent) 2-methoxyallyl bromide *(19b)* formed 2-methoxyallyl trifluoroacetate at room temperature, whereas 2-methylallyl bromide reacted at temperatures well below 0 C[17]. Furthermore, various attempts to generate the 2-methoxyallyl cation *(21)* as a long-lived species by standard procedures have failed. Apparently, the precursor *(19b)* has proved so sensitive that only complex mixtures resulted in which nothing resembling an allyl cation could be identified[18].

It has been shown more recently that cycloadditions of the 2-methoxyallyl cation can be carried out, admittedly not before removing some formidable experimental obstacles. Thus, the starting material had to be restrained from polymerization, which in the presence of the silver salt and the silver halide formed during the reaction, tended to produce a solid, intractable black mass together with the organic material. The following precautionary measures were found essential.

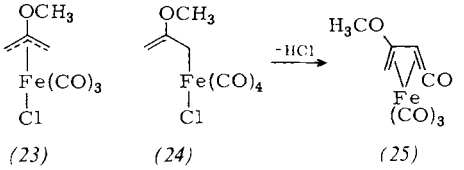
1) The silver salt should be added to the reaction mixture in small portions over an extended period (*ca.* 20 h).

2) A base or buffer compatible with the silver salt must be present to prevent accumulation of trifluoroacetic acid which in this case is harmful.

3) The reaction mixture should be kept in the dark, since silver halides are sensitive to light.

4) The most important point is that the reaction mixture must be stirred with an efficient vibromixer (100 Hz).

In this way the 2-methoxyallyl moiety could be combined with *inter alia* furan, cyclopentadiene, and 6,6-dimethylfulvene to yield the series of bicyclics *(22a)—(22c)*[19]. While bicyclo[3.2.1]oct-6-en-3-one *(22b)* had been obtained earlier in not less than six stages from norbornadiene[20], the 8-oxa analog *(22a)* had remained elusive and—being bereft of methyl substituents—would not be accessible by any of the other methods outlined below.



(23) *(24)* *(25)*

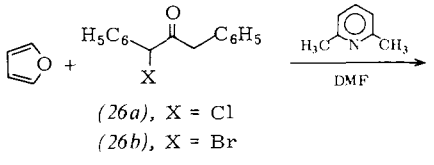
The unusual character of the 2-methoxyallyl system *(19)* is also manifest in the reactions of *(19a)* and *(19b)* with carbonylmetals. For instance, treatment of 2-methoxyallyl chloride *(19a)* with nonacarbonyldiiron does not afford the π-allyl complex *(23)* as one might have expected, but instead bright yellow volatile crystals of 3-methoxy-1,3-

butadienone(tricarbonyl)iron *(25)*. Presumably, the σ-allyl complex *(24)* is an intermediate which instead of leaking into the usually preferred π-allyl compound *(23)* is capable of forming *(25)* *via* renewed carbonylation. The organic ligand of *(25)* is a vinylketene and belongs to a class of interesting and highly reactive π systems which have not yet been studied in detail[21].

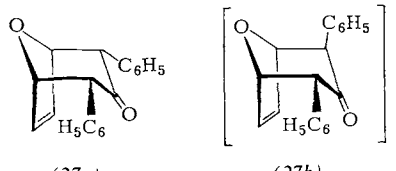
To summarize, the methoxy grouping at the central carbon appears to deactivate the allyl system toward S_N1 as well as S_N2 reactions. In this respect, the situation can be compared with the *meta* deactivation of electrophilic aromatic substitution by a methoxy group. Owing to the electron-attracting inductive effect of oxygen, the Hammett substituent constant of methoxy is positive ($\sigma_{meta} = 0.12$, more strongly electron-withdrawing than hydrogen), while σ_{para} is, of course, negative (-0.27)[22].

4. α,α′-Dihalo Ketones

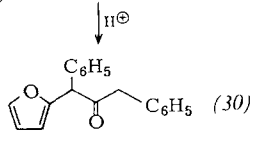
Some of the experimental difficulties in handling allyl cations can be greatly alleviated by attaching phenyl groups to the allylic termini. In an ingenious experiment published in 1962 *Fort* treated α-chlorodibenzyl ketone *(26a)* with 2,6-lutidine in the presence of furan (DMF at 25 C, 4 d) and showed that a seven-membered adduct was formed,



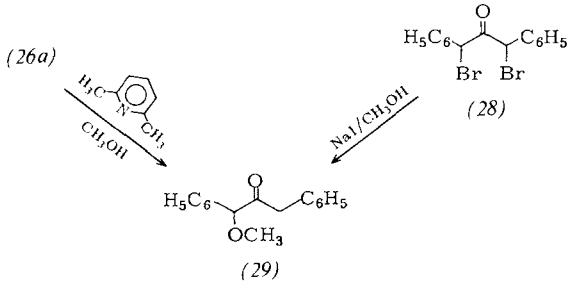
(26a), X = Cl
(26b), X = Br

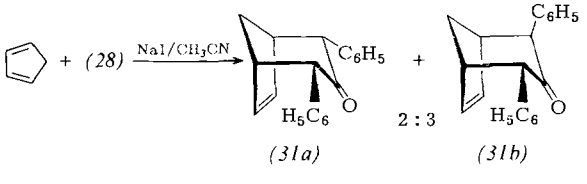


(27a) *(27b)*



(30)

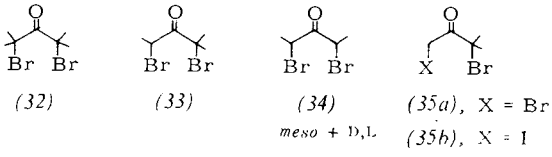




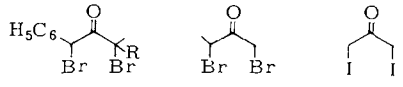
(31a) *(31b)*

the phenyl groups of which were *cis*[23a]. The same author had also reported earlier that the reaction of *(26a)* with 2,6-lutidine in methanol or the reduction of the dibromo ketone *(28)* with iodide ion in methanol yielded the α-methoxyketone *(29)*[23b]. Although it was not fully recognized at that time, there can be little doubt now that the formation of the seven-membered ring must be placed into the class of cycloadditions [eq. (3)].

Soon afterwards *Cookson* assigned the two phenyl groupings to the *cis* diequatorial positions as in [*(27a)*] and showed that this adduct could also be obtained from the dibromo ketone *(28)* and furan by treatment with (i) sodium iodide in boiling acetonitrile or acetone, (ii) mercury, or (iii) on boiling with zinc-copper couple in acetonitrile for two days; under these particular conditions varying amounts of the equatorial, axial epimer *(27b)* and the α-furyl isomer *(30)* were also isolated; *(27a)* was reported to yield *(27b)* as well as *(30)* on exposure to acid. With cyclopentadiene under fairly vigorous conditions the adducts *(31a)* and *(31b)* were found to be formed in a ratio of 2 : 3[24].



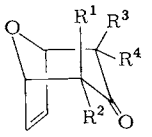
(32) *(33)* *(34)* meso + D,L *(35a)*, X = Br *(35b)*, X = I



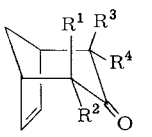
(36a), R = CH_3 *(37a)* *(37b)*
(36b), R = H

Scheme 3. α,α′-Dihalo ketones *(32)*—*(36)* can be used as precursors of allyl cations; *(37a)* and *(37b)* cannot.

As soon as the dihalo ketone is deprived of its phenyl groups, the conversion into an allyl cation is necessarily more difficult. However, by using the proper combination of dehalogenating agent and solvent it could be shown that cycloadditions proceeded more generally and under milder conditions than had previously been thought possible. In experiments going back about four years (cited in ref. [25]) we investigated the feasibility of forming allyl cations from model dihalo ketones (Scheme 3). Whereas 1,3-diiodoacetone *(37b)* and also *(37a)* showed no tendency to enter into the desired reaction, the dihalo ketones *(32)*—*(36)* were found to be suitable provided one used a reactive zinc-copper couple in combination with the right medium. After experiments with a variety of solvents, it became clear that glyme is advantageous, since it is inert to the reactants and readily forms a stable solid with the zinc halide which is liberated during the dehalogenation. In this way, the cycloaddition could be carried out at 25 C or below. By using furan and cyclopentadiene, respectively, as diene components a wide range of 8-oxabicyclo[3.2.1]oct-6-en-3-ones *(38)*—*(43)* and bicyclo[3.2.1]oct-6-en-3-ones *(46)*—*(51)* (Table 1) was obtained[26].



(38)–(45), (22a)



(46)–(53), (22b)

of the hybridization of the carbonyl carbon. If the angle is small as in cyclopropanone and cyclobutanone, the carbonyl carbon is relatively electron-attracting and the carbonyl stretching frequency is quite high, *i. e.* 1813[29a] and 1775 cm^{-1}[29b], respectively[*]. Cyclohexanones in nonpolar solvents absorb in the range 1709—1714 cm^{-1} and on continued expansion of the angle as in, say, medium rings the carbonyl stretching frequency drops further[30]. Accordingly, the observed reduction in carbonyl stretching in bicyclo[3.2.1]oct-6-en-3-ones suggests an expansion of the C—CO—C bond angle, which in this case can be brought about by deformation of the six-membered ring and flattening toward a half-boat. Now one can see that such flattening will also blur the environmental distinction of axial and equatorial methyl groups, and this seems indeed borne out by the chemical shift difference Δ. From the data in Table 1 it is evident that Δ is consistently smaller for the carbobicyclics than for the oxabicyclics, in accord with the postulated greater deformation of the cyclohexanone chair.

Table 1. Selected IR and NMR data of 8-oxybicyclo[3.2.1]oct-6-en-3-ones *(38)—(45)* and *(22a)* and the bicyclo[3.2.1]oct-6-en-3-ones *(46)—(53)* and *(22b)*.

R^1	R^2	R^3	R^4	Cpd. Ref.	νCO [cm^{-1}]	Δ [a]	Cpd. Ref.	νCO [cm^{-1}]	Δ [a]
CH_3	CH_3	CH_3	CH_3	*(38)* [26, 27a–27d]	1710	0.42	*(46)* [26]	1695	0.21
H	CH_3	CH_3	CH_3	*(39)* [26, 27e]	1715	0.38	*(47)* [26]	≈1707	0.18
CH_3	H	CH_3	CH_3				*(48)* [26]	≈1707	obscured
H	H	CH_3	CH_3	*(40)* [26, 27c]	1720	0.34	*(49)* [26, 27c]	1714	0.17
H	CH_3	H	CH_3	*(41)* [26]	≈1715		*(50)* [26]	≈1710	
H	CH_3	CH_3	H	*(42)* [26]	≈1715				
CH_3	H	CH_3	H	*(43)* [26]	≈1715		*(51)* [26]	1710	
H	H	H	CH_3	*(44)* [27c]	≈1717		*(52)* [27c]	1720 [b]	—
H	H	CH_3	H	*(45)* [27c]	≈1717		*(53)* [27c]	1720 [b]	—
H	H	H	H	*(22a)* [19]	1720		*(22b)* [19]	1713	—

[a] $\Delta = \delta_{axial} - \delta_{equatorial}$.
[b] The carbonyl stretching frequency reported in ref. [27c] must be too high, since the band should come at *lower* frequency than that in the corresponding oxa analog; cf. text and other bicyclics in this Table.

4.1. Configurational Assignment and Conformation of Bicyclo[3.2.1]oct-6-en-3-ones and 8-Oxabicyclo[3.2.1]oct-6-en-3-ones

Although the compounds of Table 1 represent a structurally simple class of bicyclics, they had been largely unknown and consequently, their configuration as well as conformation had to be deduced.

Axial protons and methyl protons generally resonate upfield from the signals of the corresponding equatorial protons[28]. In striking contrast, the axial proton and methyl group which are α to the carbonyl moiety of a cyclohexanone chair, were found to appear *downfield* from the equatorial proton and methyl group, respectively. A simple stereoelectronic effect, *i. e.* overlap or hyperconjugation of the axial σ bond with the π system of the carbonyl group, can be invoked to account for these observations[26].

A more detailed inspection of the spectral data of the bicyclics in Table 1 brings to light some interesting conformational subtleties, a grasp of which is useful for an understanding of the mechanistic discussion to follow (Section 9.2). Two experimental facts stand out clearly.

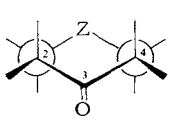
1) The IR carbonyl stretching frequency of the carbobicyclics is consistently smaller than that of the oxa analogs (cf. also Table 1, footnote [b]).

2) The chemical shift difference Δ of axial and equatorial methyl protons is consistently smaller for the carbobicyclics (cf. Table 1).

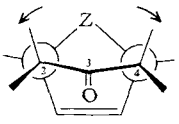
The IR stretching frequency of a carbonyl group is a function of the C—CO—C bond angle or, to rephrase,

The conformational variations of the two bicyclic systems can also be illustrated by the NMR spectrum of the parent member of each class, namely bicyclo[3.2.1]oct-6-en-3-one *(22b)* and 8-oxabicyclo[3.2.1]oct-6-en-3-one *(22a)*[19]. The axial and equatorial protons in *(22a)* appear as a well-defined AB quartet at 2.4 ppm ($J_{H_a,H_e} = 16$ Hz) and the downfield, axial protons are coupled further to the vicinal bridgehead protons ($J_{H_a,H_b} = 5$ Hz). In contrast, the α-carbonyl protons of *(22b)* coincide as an ill-resolved broad signal in the region of 2.2—2.3 ppm, *i. e.* judging by NMR they appear to have lost any distinct axial or equatorial character.

[*] *Note added in proof* (Sept. 21, 1973): According to recent studies the carbonyl frequencies of cyclopropanone and cyclobutanone appear to be even higher; cf. *W. J. M. van Tilborg*, Tetrahedron Lett. *1973*, 523.



(54)

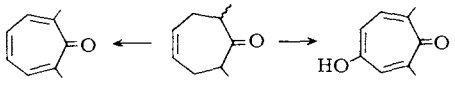


(55)

A simple mechanical model[31] seems useful for describing the differences in the two bicyclic series. On joining the 1,5-diaxial positions of a cyclohexanone chair *(54)* by an ethylene grouping the 2,4-diaxial substituents are prized apart and as a result, the chair flattens [*(55)*]. Since the methylene bridge is longer than the oxygen bridge—the carbon-carbon and carbon-oxygen bond distances are *ca.* 1.54 and 1.43 Å, respectively—deformation toward the half-boat is expected to be more pronounced in the carbocyclic series.

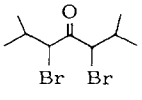
Whatever more conformational detail may come to light it is clear that the zinc-copper couple reaction enables us to introduce substituents into thermodynamically unfavorable *axial* positions. As a result bicyclo[3.2.1]oct-6-en-3-ones are now available in all their variations. α,α'-Dihalo ketones can be dehalogenated by reagents other than zinc-copper couple. Thus, dehalogenation of 1,3-dibromo-1,3-diphenylpropanone *(28)* by mercury has already been mentioned. Although metallic mercury fails to react with simple dibromo ketones such as those shown in Scheme 3, we have found that dehalogenation occurs with an excess of iodide ion in the presence of mercury or copper; the exclusion of light is desirable in this reaction (see below, Table 3 and Section 9.1.2).

In view of the great interest that must be attached to reactions of α,α'-dihalo ketones such as *(32)*—*(37)*, it is not surprising that aspects of their chemistry were investigated by other workers. Thus, the electrochemical reduction of 2,4-dibromo-2,4-dimethyl-3-pentanone *(32)* — which is particularly prone to ionization—in the presence of furan provides an alternative route to cycloadduct *(38)*[27d]. The debromination of *(32)*, *(34)*, and *(56)* with $Fe_2(CO)_9$ in the presence of conjugated dienes has also been reported: by using a bromination-debromination sequence troponoid compounds have been prepared (Scheme 4)[32].

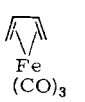


Scheme 4. Preparation of the troponoid compounds 2,7-dimethyl-2,4,6-cycloheptatrien-1-one (in two steps) and the 4-hydroxy derivative (in three steps) from 2,7-dimethyl-4-cyclohepten-1-one.

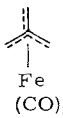
Instead of employing $Fe_2(CO)_9$ the use of diene(tricarbonyl)-iron complexes such as *(57)* has been suggested[32]; apart from ferrocene, *(57)* is perhaps the best known and most investigated organoiron complex[33].



(56)

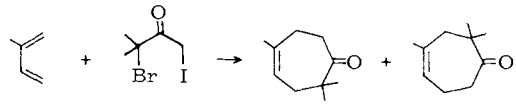


(57)



(58)

Another organoiron complex, namely trimethylenemethyl-(tricarbonyl)iron *(58)*, has been irradiated in the presence of cyclopentadiene to yield 3-methylenebicyclo[3.2.1]oct-6-en-3-one *(7)* among a complex mixture of products[34]. The direct combination of the 1,1-dimethyl-2-oxyallyl cation[*] with isoprene is of special interest. Although the dehalogenation of *(35b)* is relatively difficult, it could be accomplished on a column filled with zinc-copper couple (see below), and in the presence of isoprene gives rise to karahanaenone *(59)* and the isomer *(60)* in the ratio

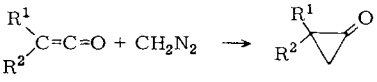


(35b) (59) (60)

2.8:1[35]. Karahanaenone is a pleasant-smelling natural product and had previously been isolated from oil of hops[36], whereas its isomer *(60)* was unknown. By using a modified debromination procedure, *i.e.* sodium iodide in the presence of mercury or copper instead of zinc-copper couple, *(59)*, *(60)* (in the ratio 1:1.2), and at least three other monocyclic monoterpenoids $C_{10}H_{16}O$ were formed in a single experimental stage (see Section 9.3)[35].

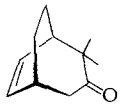
5. Cyclopropanones

The synthesis of cyclopropanone *(61a)* by treating an excess of ketene with diazomethane was discovered in 1932[37], but then seemed to sink into almost complete oblivion until *Turro* extended it to methylated cyclopropanones[29a]. Although doubt remains whether the combination of cyclopropanones and conjugated dienes actually proceeds *via* allyl cations (cf. Section 9.1.4.), there exists at least a formal relationship with the other cycloadditions described in this paper insofar as seven-membered rings may be formed. 2,2-Dimethylcyclopropanone *(61c)* which can be prepared and handled most easily, combines with furan, 2-methyl- and 3-methylfuran, furfural[27c], 2-methoxycarbonylfuran[27e], cyclopentadiene, 6,6-dimethylfulvene, and *N*-methylpyrrole.

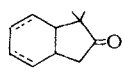


(61a), $R^1 = R^2 = H$
(61b), $R^1 = CH_3$, $R^2 = H$
(61c), $R^1 = R^2 = CH_3$

Interestingly, cycloaddition of *(61c)* to cyclohexadiene already seems difficult, *(62)* and *(63)* being tentatively identified products only. Methylcyclopropanone *(61b)*



(62)



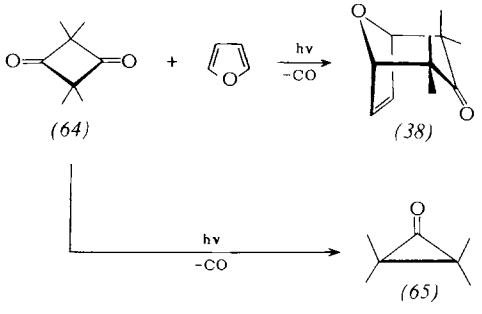
(63)

[*] Concerning the formulation of "oxyallyl", see formula *(96)* in Scheme 8 and formula *(101)*.

reacts with furan and cyclopentadiene to give the epimeric pairs *(44)* and *(45)* (ratio *ca.* 4:1) and *(52)* and *(53)* (ratio *ca.* 2:1), respectively[27c].

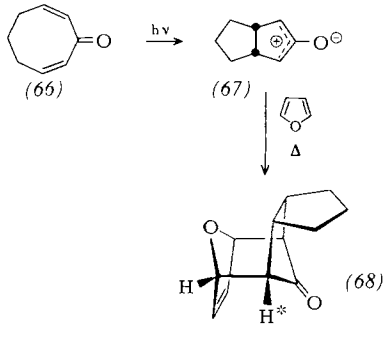
Trimethylcyclopropanone, which cycloadds to furan, can only be prepared with some difficulty by analogy with *(61a)*—*(61c)*[27e], presumably because diazoethane is less nucleophilic than diazomethane. The parent cyclopropanone *(61a)* is very prone to nucleophilic attack and polymerization and does not cycloadd to conjugated dienes at all, not even to furan[29a].

The first cycloaddition of a cyclopropanone was reported by *Cookson*[27a] who photolyzed tetramethylcyclobutanedione *(64)* in furan to obtain *(38)*; tetramethylcyclopropanone *(65)* is a known photoproduct of *(64)*, but cannot be obtained by analogy with *(61a)*—*(61c)*. Alternatively, the adduct *(38)* was formed under purely thermal conditions, *i. e.* by keeping *(65)* together with furan at room temperature[27c].



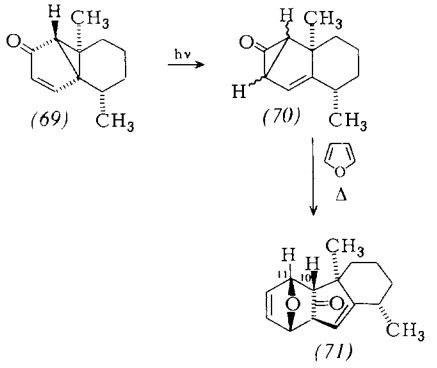
(64) *(38)* *(65)*

An interesting variation on the oxyallyl theme was provided by the irradiation of 2,7-cyclooctadienone *(66)* in furan at −78 °C, which furnished adduct *(68)*; this compound could also be prepared by irradiating *(66)* in an inert solvent at −78 °C, turning off the light source and then adding furan. The mesoionic species *(67)* has been postulated as an intermediate, although it should be borne in mind that the corresponding tricyclic cyclopropanone valence isomer is presumably more stable (cf. also *(70)* and Scheme 9). On the basis of the vicinal coupling constant $J_{H,H} = 3.5$ Hz, it has been proposed that the bridging oxygen and the carbonyl bridge of the tetracycle are *anti* to each other, as shown in *(68)*[38]. This assignment is now strongly supported by the chemical shift of the methine protons α to carbonyl (δ = 2.1 ppm), which is suggestive of an equatorial proton.



(66) *(67)* *(68)*

Irradiation of the homodienone *(69)* afforded the annelated cyclopropanone *(70)*, which was detected in an IR

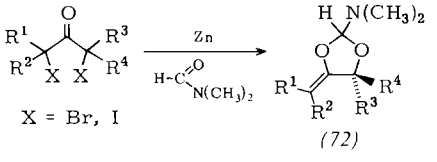


(69) *(70)* *(71)*

cell at −190 °C; cycloaddition to furan gave *(71)* and occurred subsequently as a dark reaction[39]. On the basis of the reported 10-H chemical shift (δ = 2.00 ppm) and the vicinal coupling constant ($J_{10\text{-H},11\text{-H}} = 1.5$ Hz) proton 10-H can now be assigned to the equatorial position as shown, or to restate, the tetrahydropyranone moiety in *(71)* is present in a frozen chair form [cf. also *(79)*].

6. Synthesis and Reactions of New Heterocycles

From the very beginning it seemed desirable to develop as diverse a range of allyl cation progenitors as possible. The dehalogenation of α,α′-dihalo ketones in the presence of conjugate dienes is certainly very convenient from a preparative point of view—and zinc-copper couple is a cheap reagent—but it tells us relatively little about the structure of the reactive intermediate. In this respect the dehalogenation of α,α′-dihalo ketones in dimethylformamide is an informative complementary reaction, because the organozinc intermediate is now captured in a different, yet characteristic manner (see also Section 9.3).



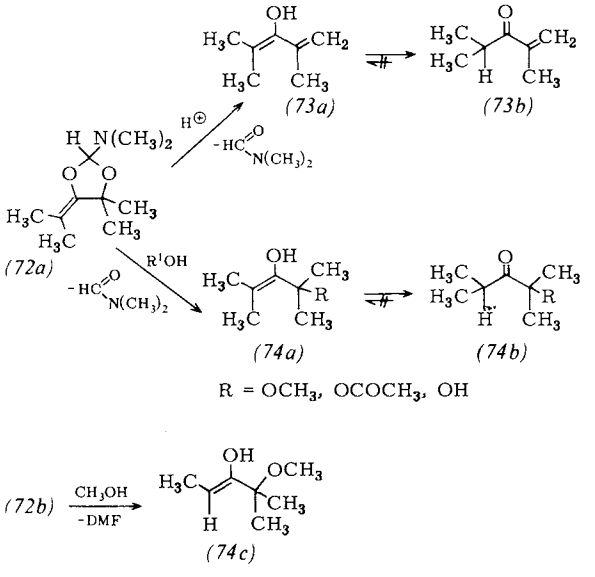
(72)

Scheme 5. Synthesis of the 4-alkylidene-2-dimethylamino-1,3-dioxolanes *(72a)*–*(72e)* from α,α′-dihalo ketones. *(72a)*, $R^1 = R^2 = R^3 = R^4 = CH_3$; *(72b)*, $R^1 = R^3 = R^4 = CH_3$, $R^2 = H$; *(72c)*, $R^1 = R^3 = CH_3$, $R^2 = R^4 = H$; *(72d)*, $R^1 = R^4 = CH_3$, $R^2 = R^3 = H$; *(72e)*, $R^1 = R^2 = H$, $R^3 = R^4 = CH_3$.

Thus we could show quite generally that α,α′-dihalo ketones such as *(32)*—*(35)*, which on dehalogenation with zinc-copper couple cycloadd to conjugated dienes, combine with dimethylformamide and dimethylacetamide to yield 4-alkylidene-2-dimethylamino-1,3-dioxolanes *(72a)*—*(72e)* (Scheme 5). It comes as no surprise that these heterocycles are highly sensitive to heat, moisture, light, and oxygen, and that their purification and isolation at low temperature proved to be difficult. Eventually, a specifically designed reactor-extractor enabled us to continuously extract the products from the dimethylformamide mother liquor with pentane or isopentane at −40 to −50 °C[40]. By cooling the stirred pentane extract to

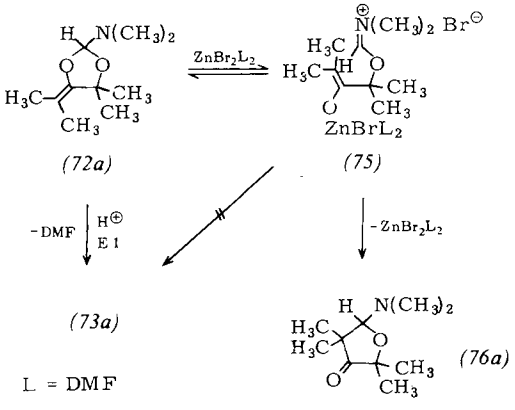
−78 °C overnight, the residual dimethylformamide could be frozen out to give the five-membered rings practically free from impurities[40b].

4-Alkylidene-2-dimethylamino-1,3-dioxolanes *(72)* can be regarded as cyclic α-aminoacetals of nonexistent (cf., however, ref. [41b]), 2-hydroxyallyl alcohols and in many reactions provide a convenient source of the oxyallyl moiety. From a mechanistic point of view the cycloadditions of *(72b)* and *(72c)* + *(72d)* to furan are of special interest, since they yield the bicyclics *(39)* and *(41)*, respectively, with high stereospecificity (cf. Section 9.2).



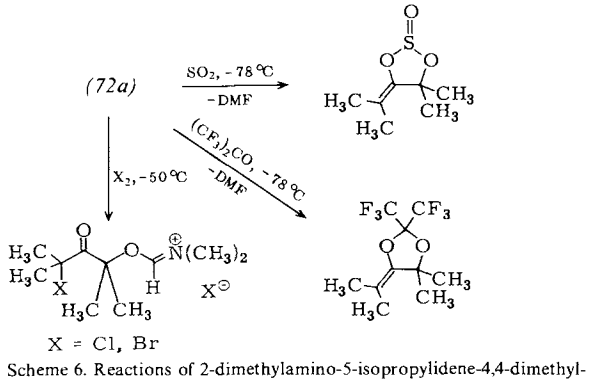
It is worthy of note that the isopropylidene-substituted heterocycle *(72a)* and furan do not give any discernible amounts of seven-membered adduct in a variety of conditions[26,40b]. Instead, *(72a)* is rather susceptible to formation of the simple aliphatic enol *(73a)*, which has been identified spectroscopically as well as chemically and which can be handled under conventional conditions at room temperature before it rearranges irreversibly into ketone *(73)*. Quite generally, by treating heterocycle *(72a)* with acidic reagents ranging from methanol to acetic acid, we succeeded in obtaining a bevy of simple aliphatic enols of the general structure *(74a)* in high concentrations (0.5 to > 1 mol/l) at room temperature[41b]. The comparative kinetic stability of these enols can be attributed to several factors including the high reactivity of the precursor and hence the mild experimental conditions of their genesis, the solvent type, and the complete alkylation of the enolic double bond. On treating heterocycle *(72b)* with methanol and *O*-deuterated methanol the simple dialkylated enol *(74c)* and its *O*-deuterio analog, respectively, could be generated and identified. However, the lifetime of these enols is considerably shorter, being *ca.* 10 min at room temperature[41c].

Electrophilic attack of the electron rich enolate oxygen in heterocycle *(72a)* is not restricted to that by protons. Aggressive dipolarophiles such as liquid sulfur dioxide and hexafluoroacetone react at −78 °C with quantitative exchange of dimethylformamide. Less electrophilic reagents like trichloroacetaldehyde and diethyl azodicarboxylate require longer reaction times and may give varying amounts of the α,β-unsaturated ketone *(73b)*[42]. On contact with perdeuteriodimethylformamide at −15 °C for 18 days, *(72a)* releases the dimethylformamide moiety and cleanly incorporates the labeled compound[41b]. Bromine and chlorine react at −50 °C or below with ring-opening to form the corresponding ammonium halides (Scheme 6)[42].

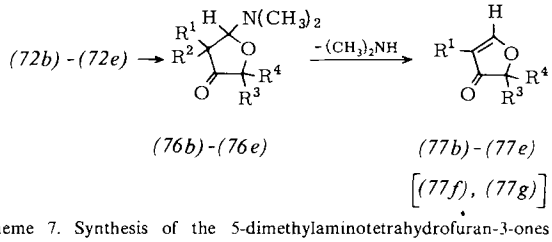


Interestingly, the E1 route to the enol *(73a)* can also be blocked when heterocycle *(72a)* is stirred in dimethylformamide in the presence of zinc bromide. In these conditions intramolecular alkylation of the highly crowded enolate moiety can be forced, the cyclic α-aminoether *(76a)* being formed after one week at room temperature (cf. Section 9.3).

The rearrangement exemplified by the formation of *(76a)* from *(72a)* is a general reaction of 4-alkylidene-2-dimethyl-



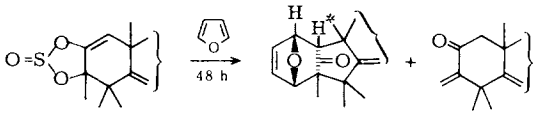
Scheme 6. Reactions of 2-dimethylamino-5-isopropylidene-4,4-dimethyl-1,3-dioxolane *(72a)* with electrophiles.



Scheme 7. Synthesis of the 5-dimethylaminotetrahydrofuran-3-ones *(76b)*—*(76e)* and the 3(2*H*)-furanone *(77b)*—*(77e)*. *(76b)*, $R^1=R^3=R^4=CH_3$, $R^2=H$; *(77b)*, $R^1=R^3=R^4=CH_3$. *(76c)*, $R^1=R^3=CH_3$, $R^2=R^4=H$; *(77c)*, $R^1=R^3=CH_3$, $R^4=H$. *(76d)*, $R^1=R^4=CH_3$, $R^2=R^3=H$; *(77d)* ≡ *(77c)*. *(76e)*, $R^1=R^2=H$, $R^3=R^4=CH_3$; *(77e)*, $R^1=H$, $R^3=R^4=CH_3$. *(77f)*, $R^1=C_6H_5$, $R^3=R^4=CH_3$, and *(77g)*, $R^1=C_6H_5$, $R^3=CH_3$, $R^4=H$, were prepared from *(36a)* and *(36b)* respectively.

amino-1,3-dioxolanes. The ease of this rearrangement yields insight into the behavior and nucleophilicity of model enolate ions. Thus, the ethylidene-substituted heterocycle *(72b)* did not cycloadd to furan, if these two compounds—instead of being kept together neat—were diluted with CCl_4 as solvent. In this case rearrangement into *(76b)* was the fastest reaction. For heterocycle *(72e)* the corresponding transformation occurred even more rapidly, being complete after standing overnight at room temperature. The 5-dimethylaminotetrahydrofuran-3-ones *(76b)*—*(76e)* so formed can be viewed as cyclic β-ketoamines, which are rendered even more labile by the α-ether grouping. Accordingly they lose dimethylamine readily and irreversibly to yield the 3(2*H*)-furanones *(77b)*—*(77d)*[43]. Occasionally, the formation of 3(2*H*)-furanones is so facile that the intermediacy of heterocycles *(72)* and *(76)* can only be inferred; thus, the debromination of the dibromoketones *(36a)* and *(36b)* affords *(77f)* and *(77g)* directly. 2,2-Dimethyl-4-phenyl-3(2*H*)furanone *(77f)* is a previously unknown isomer of bullatenone[44], which is isolated from *Myrtus bullata*, a shrub indigenous in New Zealand.

In principle, replacement of the phenyl group in *(77f)* by hydrogen leads to furanone *(77e)*, which in practice is obtained more conveniently from heterocycle *(72e)*. 2,2-Dimethyl-3(2*H*)-furanone *(77e)* is a sweet smelling oil, and it should be mentioned that 3(2*H*)-furanones are valued by perfumers because of their pleasant and varied odors and, furthermore, may serve as precursors for the synthesis of muscarins[43]. The reaction sequence described offers an unusually simple entry into this interesting, but also fairly sensitive class of compounds.



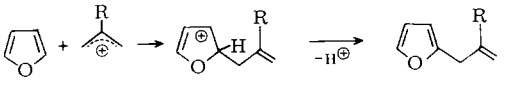
(78) *(79)* *(80)*

The compound *(78)* is formally related to the heterocycles *(72b)* and *(72c)* + *(72d)* described above in that it seems relatively reactive and combines with furan to furnish a seven-membered ring, *i. e. (79)*, and also the elimination product *(80)*[45a] (see also Scheme 6 and Section 9.1.4). On the basis of the NMR data reported ($\delta_{H^*} = 2.08$ ppm, $J_{H^*H} = 1.3$ Hz)[45b] the carbonyl group in *(79)* must be *anti* to the bridging oxygen as indicated. This assignment, like those made above, is substantiated by comparison with a wide variety of 8-oxabicyclo[3.2.1]oct-6-en-3-ones containing methylene bridges in the 2,4 positions[46].

7. The Diene Component

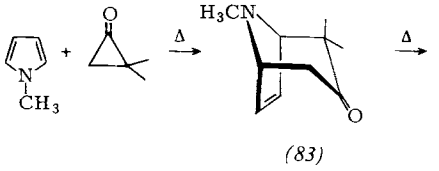
Although cyclopentadiene is somewhat more reactive, the most widely used diene component remains furan. Unlike cyclopentadiene, furan does not dimerize, and in many instances can actually be used as the solvent for the cycloaddition. Owing to the low boiling point of 31 C the excess of furan can easily be removed at the end of the reaction. Finally, the NMR spectra of the resulting 8-oxabicyclo[3.2.1]oct-6-en-3-ones are generally simple and can be interpreted readily, especially so since for any future studies a bevy of model compounds of known configuration and conformation is now available from our work[26,46].

While many allyl cations including the 2-methoxyallyl cation *(21)*[19] afford oxygen-bridged seven-membered rings with furan, it should be remembered that this is by no means valid for all allyl cations. For instance, the 2-methylallyl cation[5], the parent allyl cation[47a], the cyclopentenyl cation[47b], and others[47a] give rise to the products of electrophilic substitution, namely 2-allylfurans *(82)*. Whatever the mechanistic details of these reactions it seems clear that in the present instance an oxonium ion like *(81)* must be superior in stability to any bicyclic carbocation that may or may not be formed on the way to *(81)*[5].

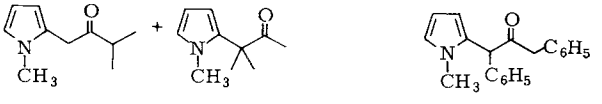


(81) *(82)*

N-Methylpyrrole and 2,2-dimethylcyclopropanone *(61c)* afford compound *(83)* which on heating rearranges into an isomeric mixture of *(84)* and *(85)*[27c,47c]. The reaction of *N*-methylpyrrole and 1,3-diphenyl-2-oxyallyl cation, generated from bis(α-bromobenzyl) ketone *(28)* and sodium iodide, has been reported to give the α-substituted derivative *(86)* directly[24b].

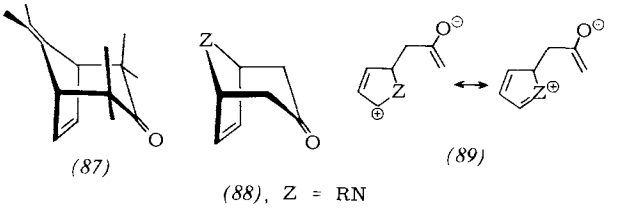


(83)



(84) *(85)* *(86)*

Cycloadditions to fulvenes can be accomplished without difficulty. For example, 6,6-dimethylfulvene has been shown to combine with 2,2-dimethylcyclopropanone *(61c)*[27c] and debromination of the ditertiary dibromo ketone *(32)* with zinc-copper couple in the presence of the same diene affords *(87)* in a clean reaction[48]; 2-methoxyallyl cation has been shown to react with fulvene as well[19].



(87) *(89)*

(88), Z = RN
(22a), Z = O
(22c), Z = $(CH_3)_2C{=}C$

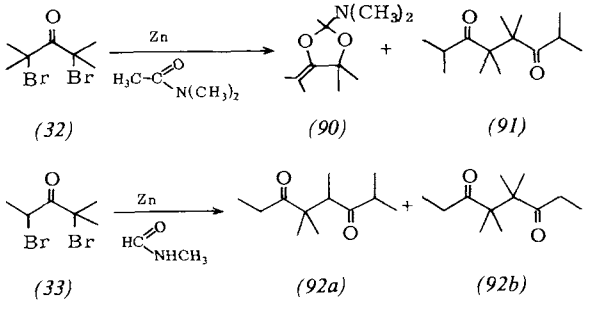
It is instructive to compare the thermal stability of the bridged 4-cycloheptenones as a function of the nature of the bridge. While dehydrotropinones such as *(88)* are relatively thermolabile, the parent 8-oxabicyclo[3.2.1]oct-6-en-3-one *(22a)* largely survives short treatment with dilute nitric acid at 60 °C and has actually been purified by sublimation under reduced pressure[19]. Nevertheless, it is clear that such compounds having an oxygen bridge do break up quite readily—especially if certain stereoelectronic requirements are fulfilled[46]—to form α-furyl derivatives. By comparison, the isopropylidene-bridged derivatives *(22c)* appear to be fairly stable, at least under nonacidic conditions. Presumably, thermal cleavage of the bicyclics *(88)*, *(22a)*, and *(22c)* proceeds *via* the zwitterion *(89)* or its protonated form. Since ammonium resonance in *(89)*, Z=RN, is more effective than oxonium resonance in *(89)*, Z=O, which in turn is probably more developed than the additional allylic resonance in *(89)*, Z=$(CH_3)_3C{=}C<$, the trend in relative stabilities is qualitatively understandable.

Cycloadditions to cyclohexadiene generally occur less readily as exemplified by the reaction with 2-methylallyl cation (*ca.* 30% yield)[5,10] and also with 2,2-dimethylcyclopropanone, where the formation of a seven-membered adduct remains to be confirmed[27c]. As expected, open-chain dienes react least readily, but given sufficiently stable allyl cations the yields are not unsatisfactory.

8. Side Reactions

8.1. Reductive Coupling

α,α'-Dihalo ketones such as *(32)*—*(35)*, which on treatment with zinc-copper couple furnish allyl cations, were found to be prone to bimolecular reductive coupling. For example, debromination of the ditertiary dihalo ketone *(32)* with zinc-copper couple affords heterocycle *(72a)* in dimethylformamide, but a solvent change to dimethylacetamide produces both *(90)* and the octanedione *(91)* (10%)[40]. If coupling is the desired reaction it can be promoted by using *N*-methylformamide as solvent which in being less nucleophilic but more acidic ($pK_a \approx 16$) than dimethylformamide and dimethylacetamide forms 1,3-dioxolanes less readily and promotes the reductive removal

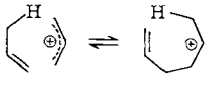


of bromine. Coupling in this manner offers a new route to 1,4-diketones from simple starting materials[40b,49].

The debromination of the mixed secondary, tertiary dibromo ketone *(33)* with zinc-copper couple in *N*-methylformamide yields all three stereoisomeric octanediones *(92a)*—*(92c)* in a ratio of 3.1 : 1.4 : 1[40b].

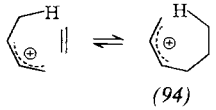
8.2. Intermolecular Hydrogen Transfer Reactions?

Since both *intra*- as well as *inter*molecular hydrogen shifts are ubiquitous in the chemistry of carbocations, the question arises whether the cycloaddition of an allyl cation might be accompanied by a bimolecular hydrogen transfer. In principle, two such reactions can be envisaged together with their converse. In reaction (4) the allyl cation takes the role of what we previously designated as the "enophile"[50], while an allyl cation containing a terminal methyl group acts as hydrogen donor in reaction (5). Were either reaction to exist it would be of intrinsic and could also be of practical interest, *e.g.* in cationic polymerization of conjugated dienes.



(4)

(93)



(5)

(94)

Using the conditions previously shown to be optimum for the cycloaddition of a simple allyl cation to conjugated dienes[10], the 2-methylallyl cation was generated from 2-methylallyl iodide and silver trifluoroacetate in isopentane at −78 °C in the presence of potential ene components such as cyclopentene, 1-pentene, 2-methoxypropene, and also more efficient hydride donors, namely 1,4-cyclohexadiene, 2,5-dihydrofuran, and cycloheptatriene. Interestingly, in no instance did we observe any defined products apart from 2-methylallyl trifluoroacetate[17]. As far as we can tell, reaction *(4)* to give cation *(93)* did not occur under any of our conditions. Presumably the energy price for carbon-hydrogen bond breaking and the stringent geometric demands of the cyclic transition state[50] are too high and not met by the gain in σ-bond energy on potential formation of the carbon-carbon bond. However, the possibility should not be discounted that reaction (4) may still come to light, perhaps as an *intra*molecular variant which optimizes orbital overlap.

9. Reaction Mechanism

9.1. Structure of the Reactive Intermediate

The ultimate objective of any mechanistic study centers on the potential energy surface of the reaction concerned. In the present instance our first task must be to elucidate the structure of the reactive three-carbon unit that com-

bines with the diene. Here we will have to draw on as wide a range of reactions as possible and scrutinize not only the cycloaddition itself, but also circumstantial evidence. Once the structure of the two π reactants and that of the products are known, it should be possible to interpolate the structure of the intervening transition state (cf. Section 9.2). An appreciation of the theoretical background will enable us to use the new reactions to their best purpose and to introduce variations in technique.

9.1.1. The Silver Salt Route

From a mechanistic viewpoint the silver salt reaction is the least ambiguous and, in point of fact, the cycloadditions realized[5,10,19] come closest to the prototype (3). Since cyclopentadiene was found not to influence the rate of formation of the silver halide, the reactive intermediate is clearly an allyl cation, which is formed in an S_N1 like reaction[7].

Now carbocations should be viewed together with their counterion and solvent rather than in isolation. According to the Winstein heterolysis scheme (Fig. 1) a covalent substrate R—X ionizes and dissociates with formation of (i) the contact ion pair, (ii) the solvent separated ion pair, and finally (iii) the free, solvated ions.

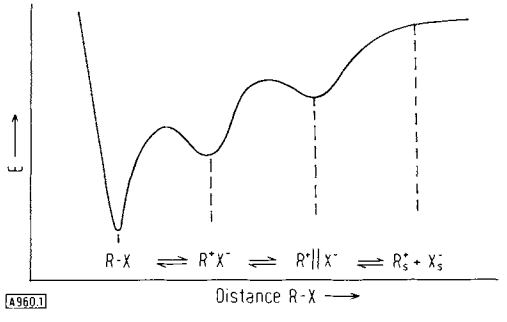
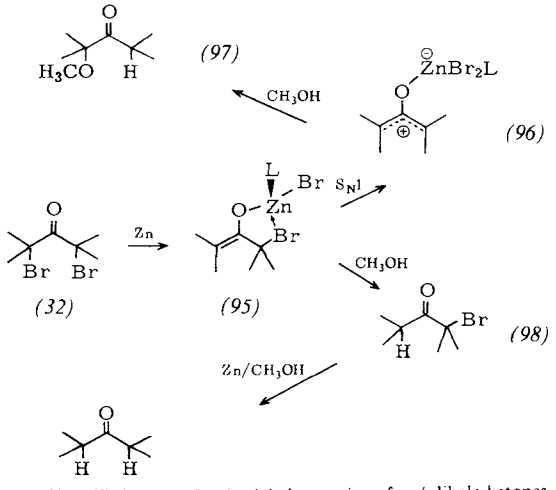


Fig. 1. Schematic energy profile for the heterolysis of an alkyl halide RX. E = potential energy. R—X = covalent substrate. R^+X^- = contact ion pair, $R^+||X^-$ = solvent-separated ion pair, $R_s^+ + X_s^-$ = free, solvated ions.

Under the prevailing heterogeneous conditions of our reactions the mechanistic situation seems less clear. If a conventional contact ion pair were involved, it would be positioned still relatively low down on the potential energy surface of heterolysis and hence might be expected to show but enfeebled reactivity and also to collapse to covalent ester. In fact, it was rather surprising to find that treatment of 2-methylallyl iodide with silver trichloroacetate in the presence of cyclopentadiene—admittedly a very reactive diene component—gave the cycloadducts *(6)* and *(7)* and less than 1% of 2-methylallyl trichloroacetate[5]. On the other hand, under homogeneous conditions—*e.g.* in ether—the yields of cycloadduct were lower, and at least the very reactive allyl cations which we used were found to form substantial amounts of covalent ester. Why the heterogeneous method is successful, is still not completely clear, but further discussion will be found elsewhere[10].

9.1.2. α,α'-Dihalo Ketones

Starting from ketones, α,α'-dibromo ketones are readily available, yet surprisingly little work[24b,51]—and none of it systematic—had been done on these compounds when we began our own investigations. From the outset it seemed desirable to obtain information which would shed light on the nature of the organometallic intermediates and would go beyond the cycloaddition to conjugated dienes.

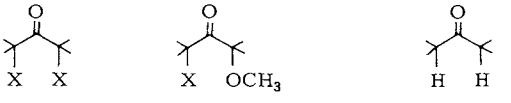


Scheme 8. Simplified scheme for the dehalogenation of α,α'-dihalo ketones with the zinc-copper couple in the presence of methanol. L = CH_3OH.

The dehalogenation of α,α'-dihalo ketones with zinc-copper couple in *methanol* has been shown to produce not only the parent ketone, but also α-methoxy ketone. This observation could appear as quite trifling, were it not for the fact that the α-methoxy ketone cannot arise by methanolysis of the starting dihalo ketone, which is inert to methanol under these conditions. It is perhaps even more interesting that the α-methoxy ketone is formed *regioselectively* in that *e.g.* the dihalo ketones *(33)* and *(35a)* + *(35b)* give rise to just one of two possible stereoisomers, which bears the methoxy moiety at the more alkylated carbon terminus (see Table 2)[52].

The dehalogenation of α,α'-dihalo ketones with zinc-copper couple in *dimethylformamide* yields 2-dimethylamino-4-

Table 2. Dehalogenation of α,α'-dihalo ketones with a zinc-copper couple in methanol at −5 to 0 °C (Schemes 3 and 8) [52].



Dihalo ketone (type A)	Products (rel. yield) α-methoxy ketone (type B)		ketone (type C)
(32)		72%	28%
(33)		76%	24%
(35a)	−35 °C:	19%	81%
	−5 °C:	14%	86%
(35b)	−35 °C:	33%	67%
	−5 °C:	5%	95%
(34)		62%	38%
(37a)	−35 °C:	0%	100%
	0 °C	0%	100%
(37b)		0%	100%
(36a)		84%	16%
(28)		100%	0%
(36b)		28%	72%

methylene-1,3-dioxolanes[40]. Interestingly, once again the dihalo ketones *(33)* and *(35a)* as well as *(35b)* react in orientationally uniform fashion in that the nucleophilic oxygen of dimethylformamide is attached exclusively to the more alkylated carbon terminus in the product, giving heterocycles *(72b)* and *(72e)*, respectively. Since the structural reorganization of the organozinc intermediate is less extensive here than in the trapping with methanol, a second stereochemical feature comes to light. By measuring the aromatic solvent induced shift (ASIS) for the complete series of heterocycles *(72a)*—*(72e)* it could be demonstrated beyond doubt that the methyl group of the exocyclic ethylidene moiety in *(72b)*, *(72c)*, and *(72d)* is present in one configuration only, which is *cis* to the vicinal oxygen[40].

What then is the role of the metal in this and related reactions of α,α'-dihalo ketones?

Clearly, it has to fulfil several functions. First, a metal such as zinc can readily donate its electrons to form the zinc enolate *(95)* as an intermediate[26,40,52]. In order to account for the stereospecific formation of heterocycles *(72b)*—*(72d)*, the intermediate *(95)* must be generated stereospecifically, at least at low temperatures, in that the methyl group of any ethylidene moiety will be *cis* to the vicinal OZnBr grouping. In the critical stage of the reaction the zinc enolate *(95)* ionizes to give the allyl cation *(96)*, here designated as "zinc oxyallyl" which will wind up as 1) α-methoxy ketone in methanol, 2) five-membered heterocycle in dimethylformamide and dimethylacetamide, 3) 1,4-dione in the presence of an excess of zinc enolate and, of course, 4) seven-membered carbocycle in the presence of conjugated diene.

As to the debromination in methanol it seems clear that the postulated zinc enolate is a finely balanced system in that it contains a) an electron-rich enolate grouping[*] which can be reduced *via* monobromoketone *(98)* into the parent ketone and b) an electrophilic zinc moiety which serves to extract bromide ion to form the desired carbocation (Scheme 8).

A priori, unsymmetrically substituted dihaloketones, such as *(33)* and *(35a)* + *(35b)* can form two zinc enolates and the question arises which isomer if any is favored thermodynamically. It has been shown in another context that thermodynamically unstable *enols* can be generated and observed the more readily, the more highly alkylated the enolic double bond[40b,41b]. Hence, if enols are to be taken as models for the corresponding zinc enolates, it seems likely that it is the more alkylated zinc enolate which is thermodynamically the more stable, and also formed preferentially.

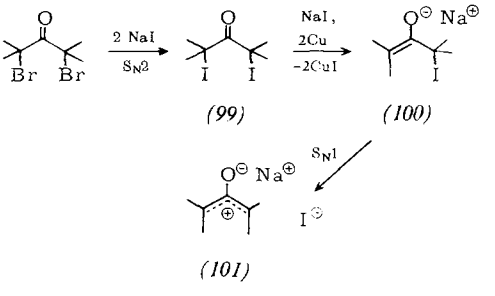
In any event, alkylation of the termini in the precursor *(95)* will also favor ionization to the allylic cation *(96)* in the next stage of the reaction. Hence the primary-tertiary dihalo ketones *(35a)* and *(35b)*, which on dehalogenation in methanol give relatively little α-methoxy ketone (Table 2), are also reluctant to form heterocycle *(72e)*, which is obtained in about 20% yield starting from *(35a)*[40b].

[*] The zinc enolate derived from 3-bromo-3-methyl-2-butanone can be acetylated with acetic anhydride at carbon; *B. K. Carpenter*, unpublished work.

Thus, it is immediately apparent that the formation of α-methoxy ketone on dehalogenation with zinc-copper couple in methanol offers an exceedingly simple and useful criterion for the feasibility of generating allyl cations and for the orientational selectivity of subsequent nucleophilic attack[52].

α,α'-Dihalo ketones which are resistant toward reaction with zinc-copper couple under ordinary conditions, can be induced to cycloadd by an important modification of technique. Adopting the very simple measure of using a long column filled with zinc-copper couple and passing the reagents down this column—if necessary several times—the dihalo ketone can be dehalogenated completely, without any remnants of possibly lachrymatory starting material in the final products. The *continuous* dehalogenation—unlike the batchwise procedure—allows repeated use of the zinc-copper couple and facilitates work up of the products[46].

The debromination of α,α'-dibromo ketones by iodide ion in the presence of mercury or copper begins with a rapid S_N2 diplacement of bromide by iodide, provided, of course, a suitable primary or secondary center is available[53]. Presumably, reductive removal of iodine by further iodide ion furnishes the enolate [*(99)*→*(100)*], the liberated iodine being trapped by mercury or copper. Subsequent ionization of *(100)* leads to allyl cation *(101)*, which, like zinc oxyallyl, combines with conjugated dienes, although the steric course of the two cycloadditions is different (cf. Table 3)[35].



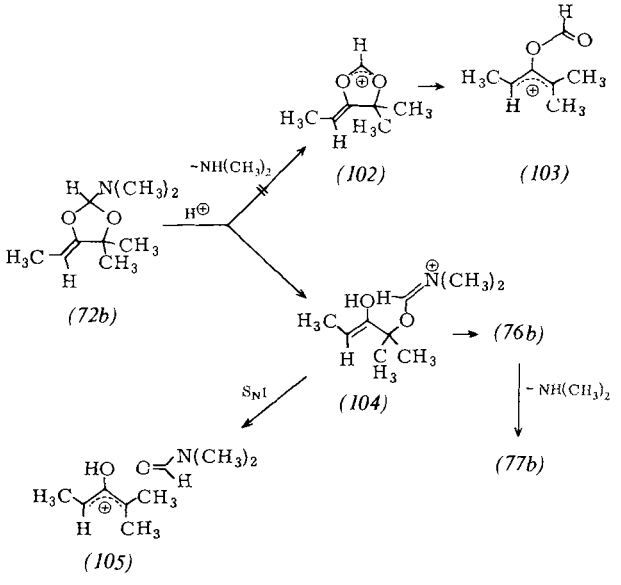
(99) *(100)* *(101)*

A few final remarks about the regioselective attack by methanol and dimethylformamide are in order. The solvolysis of allyl halides and the accompanying product spread have been studied with unusual intensity in the past[3c]. The finding that simple methylated 2-oxyallyl cations can be trapped in orientationally uniform fashion is of intrinsic interest and, to our knowledge, without precedent in solvolyses of conventional methylated allyl halides and tosylates. It should be borne in mind that: 1) all our reactions are mechanistically S_N1; 2) the zinc moiety can electrophilically assist the departure of the second bromine [*(95)*→*(96)*]; and 3) the oxygen attached to the central carbon of the allyl system contains unshared pairs of electrons which might facilitate ionization.

In effect, the intermediate which is trapped by methanol and dimethylformamide is a *delocalized* allyl cation which appears to have reached at least the solvent separated stage (cf. Fig. 1) and renounced any specific interaction with its counterion. Accordingly, it is attacked exclusively at the more electrophilic terminus, at least in the solvents methanol and dimethylformamide.

9.1.3. 4-Alkylidene-2-dimethylamino-1,3-dioxolanes

The 4-ethylidene-substituted heterocycles *(72b)* and *(72c)* + *(72d)* do not cycloadd to furan when using scrupulously dried and distilled diene. In contrast, on mixing the heterocycles with *commercial* furan, the bicyclics *(39)* and *(41)*, respectively, are formed. The cycloaddition can also be slowed down or suppressed altogether in the presence of 2,6-lutidine. It is also pertinent that formation of the enol *(73a)* from heterocycle *(72a)* is extremely sensitive to traces of acid and occurs spontaneously in commercial dimethyl sulfoxide and carbon tetrachloride, but not in spectrograde carbon tetrachloride or dry pentane[41].



During the formation of cycloadducts *(39)* and *(41)* from *(72b)* and *(72c)* + *(72d)* one observes that dimethylamine is liberated[26]. Since protonation of the amino nitrogen followed by loss of amine is a general reaction of simple 1-aminoacetals[54], one could take it as a foregone conclusion that the dioxolenium ion *(102)* is formed *en route* to allyl cation *(103)*. However, by using heterocycle *(72b)* and freeing it from dimethylformamide by the freezing-out technique it could be demonstrated more recently that *(39)* and dimethylformamide were formed in equimolar quantities, the remaining product (*ca.* 50%) being the 3(2*H*)furanone *(77b)*[40b]. Consequently, it seems more likely that the reactive species entering into the cycloaddition is the 2-hydroxyallyl cation *(105)*, which probably still interacts weakly with dimethylformamide (see below). In any event, ammonium resonance in *(104)* should be superior to oxonium resonance in *(102)*[*].

Furthermore, the 1,3-dimethyl-2-oxyallyl cation arising from heterocycles *(72c)* + *(72d)* must be different from that formed on debrominating 2,4-dibromo-3-pentanone *(34)* with zinc-copper couple; note that the two reactions give a different ratio of *cis* diequatorial epimer *(41)* to *cis* diaxial epimer *(43)* (Table 3, No. 1 and 3).

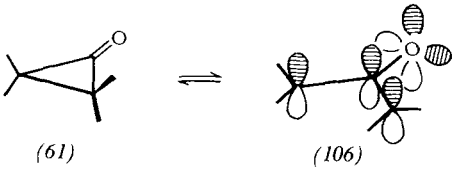
[*] Interestingly, even anhydrous hydrogen chloride in CCl_4 converts heterocycle *(72a)* quantitatively into α-chloro ketone, no dimethylamine or its hydrochloride being observed [40b].

We are now prepared to return to the isopropylidene substituted heterocycle *(72a)* which does not combine discernibly with furan under a variety of conditions, but instead affords the enol *(73a)*. It is hardly likely that a steric effect operates here, since the corresponding ditertiary dihalo ketone *(32)* can be debrominated with zinc-copper couple in the presence of furan to yield the bicyclic compound *(38)* very smoothly. Two factors appear to be responsible for these contrasting results: first, zinc oxyallyl *(96)* generated *in situ* from *(32)* should be more reactive than the corresponding 2-hydroxyallyl cation arising from heterocycle *(72a)*, and therefore combine more readily with the diene component. Secondly, dimethylformamide is more basic than bromide ion as a leaving group, and hence abstracts one of twelve peripheral methyl protons [*(72a)* → *(73a)*].

In summary, the cumulative evidence now available points to a spectrum of allyl cations including zinc oxyallyl *(96)*, sodium oxyallyl *(101)*, and hydroxyallyl cations, which, however, do not seem to occur as free, solvated cations, but rather as solvent-separated ion pairs and contact ion pairs.

9.1.4. Cyclopropanones

Clearly, the cycloadditions discussed so far proceed *via* allyl cations, which are formed under typical S_N1 conditions in the bottleneck of the overall reaction. In contrast, cycloadditions of methylated cyclopropanones appear to be different. Kinetic studies seem to implicate furan in the rate limiting stage of its reaction with several alkylcyclopropanones; hence the question arises whether the cycloaddition starts with π-oxyallyl *(106)* or the closed form *(61)*[55].

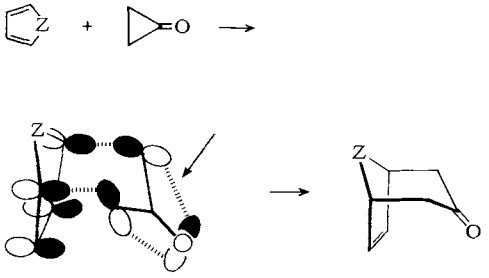


π-Oxyallyl has been proposed as an intermediate in the reaction of the heterocycle *(78)* with furan[45a]. Since the α,β-unsaturated ketone *(80)* is formed as a by-product, it is clear that at least catalytic amounts of acid must have been present in this reaction, and in the light of our work on heterocycles *(72a)*—*(72e)* it seems more likely that the reactive intermediate is actually 2-hydroxyallyl in combination with the appropriate counterion.

Theoretical conclusions and calculations as to the stability of the parent π-oxyallyl species have fluctuated. After having originally been put forward as an intermediate of the Favorskii reaction[56a], π-oxyallyl has at one time been proposed to be more stable than cyclopropanone itself[56b], but more recently been suggested to be less stable by 80 kcal/mol[56c].

The role of the carbonyl system and its electrons in the opening of (methylated) cyclopropanone(s) has never been completely clear. Because of the lone pair of electrons on oxygen, cyclopropanone can enter into reaction with the diene as a σ-component. The resulting pericycle *(107)* will be seen to contain one phase dislocation, *i. e.* it is of the

anti-Hückel[57a] or Möbius[57b] type (Scheme 9). Now, being filled with *eight* rather than six electrons, the circuit will be aromatic[57] and the reaction should be facile.



(107)

Scheme 9. Cyclopropanone as σ component in cycloadditions to conjugated dienes. The phase dislocation is indicated by an arrow.

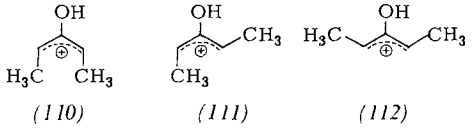
Consequently, the cycloadditions of cyclopropanones to conjugated dienes might have nothing to do with the reactions so far discussed [cf. eq. (3)] and be, strictly speaking, outside the scope of this paper.

9.2. Compact and Extended Transition States

A priori, an allyl cation can interact with a conjugated diene in the compact, boat-like transition state *(108)* or the extended chair alternative *(109)*. For an experimental distinction of the two modes at least one terminal substituent on each π-reactant is required[*].

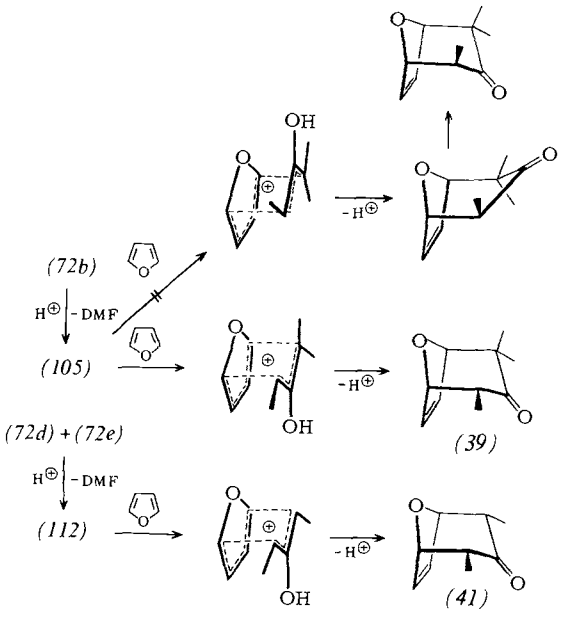
(108) *(109)*

While configurationally defined dienes are readily available, the situation is necessarily more complex with respect to the transitory allyl cation. For example, a terminally disubstituted allyl cation can exist in three configurations, namely the U form *(110)*, the sickle geometry *(111)*,



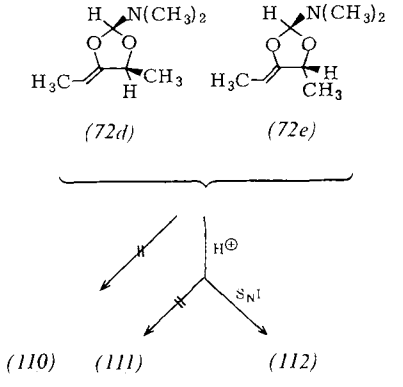
(110) *(111)* *(112)*

and the W configuration *(112)*. Ideally, one would aim to generate the allyl cation in a single and known configuration, capture it with a terminally substituted diene and finally, separate and assign any stereoisomeric adducts. By using 4-ethylidene-2-dimethylamino-1,3-dioxolanes the allyl cation geometry could be controlled. Thus, after reaction with furan, the single methyl group at C-5 of the heterocycle *(72b)* was found to have occupied the equatorial position in the adduct *(39)*. Clearly, allyl cation *(105)* is implicated as the intermediate, which combines with furan *via* the compact mode (Scheme 10).



Scheme 10. Cycloadditions *via* compact transition states.

Furthermore, the mixture of epimeric heterocycles *(72d)* + *(72e)* and furan furnished the *cis* diequatorial adduct *(41)*; thus, the intervention of the W cation *(112)*—



(72d) *(72e)*

(110) *(111)* *(112)*

rather than the sickle alternative *(111)*—is at once established; the compact course of cycloaddition is equally obvious (Scheme 10).

An extrapolation to other 2-oxyallyl cations is also feasible. For instance, debromination of 2,4-dibromo-3-pentanone *(34)*—an epimeric mixture being used—with zinc-copper couple in the presence of cyclopentadiene at 0 °C afforded the two epimers *(50)* and *(51)* in the ratio 1.67 : 1. Consequently, intervention of the W cation and leakage into the extended transition state can hardly be in doubt (cf. Table 3, No. 5)[26].

Finally, it seemed desirable to generate the 1,3-diphenyl-2-oxyallyl cation[23a,24b] and avoid any unduly harsh conditions in so doing. With furan and three different routes to the allyl cation (cf. Table 3, No. 8) intervention of

[*] In a cycloaddition involving two π-reactants any terminal substituent can be disposed *endo* or *exo* in the adduct. In order to avoid complete confusion we use the terms *endo* and *exo* to describe the configuration of *substituents*, in common with normal practice, and designate the two geometries of the π interaction as "compact" and "extended".

Table 3. Compact and extended transition states in cycloadditions of 2-oxyallyl cations [26] (see Schemes 8, 9, 10).

No.	Diene	2-Oxyallyl cation substituents	2-Oxyallyl cation precursor	Products	Transition state compact : extended
1	furan	1,3-dimethyl	heterocycle *(72d)* + *(72e)*	*(41)*	1:0
2	furan	1,3-dimethyl	halo ketone *(34)* [a]	*(41)* (94%)	≥15:1
3	furan	1,3-dimethyl	organozinc compound from *(34)*	*(41)*:*(42)*:*(43)* 81 : 9 : 10	≈8:1
4	cyclopentadiene	1,3-dimethyl	halo ketone *(34)* [a]	*(50)* (84%)	≥5:1
5	cyclopentadiene	1,3-dimethyl	organozinc compound from *(34)*	*(50)*:*(51)* 1.67 : 1	1.67:1 1.7:1 [b]
6	furan	1,1,3-trimethyl	heterocycle *(72b)*, halo ketone *(33)* [a], organozinc compound from *(33)*, cyclopropanone [27c]	*(39)*	1:0 [c]
7	cyclopentadiene	1,1,3-trimethyl	organozinc compound from *(33)*	*(47)*:*(48)* 3.8 : 1	3.8:1 2.6:1 [b]
8	furan	1,3-diphenyl	halo ketone *(26b)* [a,d], organozinc compound from *(26b)*	*(27a)*	1:0 [60]

[a] NaI induced dehalogenation in the presence of mercury or copper in acetonitrile.
[b] *R. Chidgey*, unpublished work.
[c] Reinvestigation of the preparation from organozinc compounds gave a ratio of 10:1.
[d] With 2,6-lutidine.

the W cation and the compact combination was established[60].

In discussing the results of Table 3 it must not be forgotten that a preference for one isomer by 99% represents very little in energetic terms—*i.e.* less than 3 kcal/mol—and overenthusiastic interpretation is certainly not warranted. Nonetheless, two trends seem to be discernible: 1) Cycloadditions of open-chain allyl cations to furan are more inclined to follow the compact course than those to cyclopentadiene. 2) Increasing methylation—and possibly stabilization—of the allyl cation promotes the compact transition state.

Now we recall that the six-membered ring of bicyclo[3.2.1]oct-6-en-3-ones is more prone to deformation and half-sided flattening than that of 8-oxabicyclo[3.2.1]oct-6-en-3-ones (Section 4.1). Hence, if the structure of the product is to be taken as a model for the preceding transition state, it is understandable that leakage into the extended interaction is more facile in cycloadditions to cyclopentadiene, and in fact, one may argue that the cycloadditions are subject to conformational control[58].

Yet this is probably not the complete story. Given a free choice of the two geometries *(108)* and *(109)*, the compact transition state *(108)* is unfavorable because of a weak second-order interaction, *i.e.* that of the highest occupied MO of the allyl cation and the lowest unoccupied MO of the diene[14, 59]. This interaction should become the more dominant the less stable the allyl cation (Fig. 2). In this context the formation of *cis* diaxial adduct *(43)* from the organozinc precursor (Table 3, No. 3), but not from the heterocyclic route (No. 1), is especially interesting. Since zinc oxyallyl is more electrophilic and hence less stable than the corresponding 2-hydroxyallyl species derived from the heterocyclic precursor *(72c)* + *(72d)* (Section 9.1.3), secondary orbital interaction should be more developed in the former case and be removed *via* the extended transition state, even though this has to occur at the price of placing two methyl groups into *syn*-axial

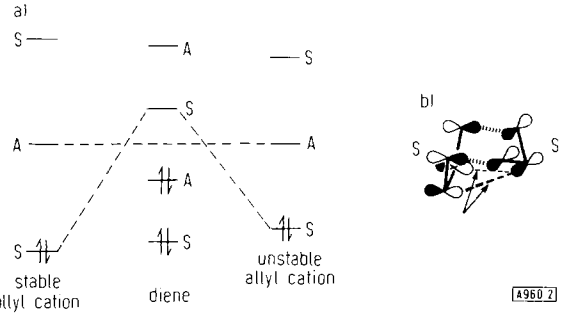


Fig. 2. Secondary orbital interaction of a diene with an allyl cation as a function of cation stability. a) The SS interaction is reduced for the more stable allyl cation, and enhanced for the less stable one. b) This compact transition state [≡ *(108)*] is less favorable than the extended one [*(109)*].

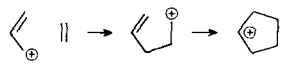
positions. On the same basis, the species derived from NaI in the presence of mercury is less electrophilic than zinc oxyallyl (cf. Table 3). Furthermore, the original work on cyclopentadiene and the 2-methylallyl cation, which showed a tendency toward an extended transition state[59], also fits nicely into the emerging pattern in that secondary orbital interaction should be especially pronounced with the highly unstable 2-methylallyl cation. In effect, one can condense our data into the rule that the more electrophilic—or the more reactive—the allyl cation, the greater the propensity toward an extended transition state.

Whatever further results may come to light, it must now be accepted as experimental fact that the steric course of the cycloaddition can be influenced and controlled by the reagents and conditions used for generating the allyl cations.

9.3. Cycloadditions of Allyl Cations to Olefins

Since allyl cations serve as π-reactants toward conjugated dienes, the question arises whether they might also combine with olefins. It has already been mentioned that intermolec-

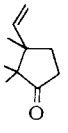
ular hydrogen transfer according to eq. (4) is as yet unobserved and presumably not very favorable on energetic as well as conformational grounds. What then is the probability of a stepwise combination of an allyl cation and an olefin to a five-membered ring (Scheme 11)?



Scheme 11. Stepwise combination of an allyl cation with an olefin.

Using the silver salt route to simple allyl cations and common olefins and dienes (cf. *e.g.* Section 8.2) we have not yet found any evidence for this reaction. In view of the general facility of forming five-membered rings, it seemed reasonable to assume that the reaction might be favored if the intermediate carbocation were sufficiently stabilized. Consequently, dimethylformamide became an obvious choice of a *hetero*olefinic component.

Although heterocycles *(72a)*—*(72e)* can formally be regarded as 1,3-dipolar adducts of oxyallyl cation to dimethylformamide, their formation can hardly be interpreted as a concerted cycloaddition. Some arguments against this reaction path have already been put forward (Section 9.1.2); the postulated stepwise formation by nucleophilic trapping of zinc oxyallyl gains further credence from the observation that heterocycle *(72a)* can be transformed into the cyclic α-amino ether *(76a)* on prolonged contact with $ZnBr_2$, *i.e.* by debrominating *(32)* with zinc-copper couple and isolating the product after one week at 25 °C rather than after 3 h at −20 °C[43]. If the ion *(75)* is the intermediate on the way from *(72a)* to *(76a)*, microscopic reversibility demands that heterocycle *(72a)* be also formed from this ion *(75)*. Overall, one can see that zinc not only serves admirably in the genesis of zinc oxyallyl from the dihalo ketone, but also in the formation of the thermodynamically more stable product *(76a)*. It should be borne in mind that under any other circumstances heterocycle *(72a)* smoothly affords the enol *(73a)* rather than *(76a)*. The deactivation of *(75)* towards the E1 route to *(73a)* recalls the reduced rate of ionization of 2-methoxyallyl halides discussed earlier. The excess of dimethylformamide can be viewed as an efficient ligand for the eventual release and disposal of $ZnBr_2$, similar to glyme which was used for the cycloadditions to conjugated dienes[26].



(113)

Given favorable electronic circumstances there seems to be no reason to exclude intermediates related to *(75)* in the reaction of 2-oxyallylic species with other olefins[61] and dienes. In fact, it has already been mentioned that the dehalogenation of the primary-tertiary dihalo ketone *(35b)* with iodide ion in the presence of mercury and isoprene yields not only the "expected" rings *(59)* and *(60)*, but also three isomeric monoterpenoids $C_{10}H_{16}O$, *i.e.*, vinylcyclopentanone *(113)* and two cyclic ethers[35]. In principle, isoprene can accommodate positive charge from the oxyallyl intermediate by forming a relatively stable dialkylated allyl cation, whereas the negative charge may be delocalized over the enolate ion. Thus the way is paved for a plethora of products. Remarkably, debromination of the di-secondary dibromo ketone *(34)* in the presence of isoprene under analogous conditions (NaI, Hg) yielded not less than twelve $C_{10}H_{16}O$ isomers[62]!

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A Planar Cyclohexane Ring: X-Ray Analysis of 9-Cyano-*anti*-dioxatris-σ-homobenzene

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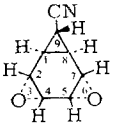
Recently a general synthetic route to trishomobenzene has been established, and some interesting properties which may arise from the strained character of the molecule reported[1]. Particular interest attaches to changes in geometry of the central cyclohexane ring when annelated to three strained small rings. We have established the structure of the molecule by X-ray analysis of 9-cyano-3,6-dioxatetracyclo[6.1.0.0^{2,4}.0^{5,7}]nonane *(1)*[2]. As far as we know, this is the first structural report on the tris-σ-homobenzene system.



(1)

Compound *(1)* crystallizes in the monocyclic space group $P2_1/c$ with $a=6.501$, $b=13.215$, $c=8.795$ Å; $\beta=115.74°$; $Z=4$; $D_{exp}=1.45$ g/cm^3, $D_{calc}=1.46$ g/cm^3. A single crystal ($0.2\times0.2\times0.25$ mm) was examined with Rigaku automatically controlled four circle X-ray diffractometer; a total of 1289 reflections (within $2\theta=55°$) were measured using $Mo_{K\alpha}$ radiation. The structure was solved by a direct method and the parameters were refined by a block-diagonal least-squares method. After several refinements, all the hydrogen atoms were found from a difference Fourier synthesis. Further anisotropic least-squares refinement (C, O, N) and simultaneous isotropic least-squares refinement (H) gave an *R*-factor of 0.048.

The most important geometrical data are shown in Figure 1. As expected, the cyclohexane ring of *(1)* has a planar conformation: the maximum deviation from the plane through C^1 to C^6 is only 0.008 Å. The dihedral angle between this plane and the cyclopropane ring (75.8°) is similar to those in *anti*-bromobishomoquinone (75—77°)[3] and 2,5-dimethyl-7,7-dicyanonorcaradiene (73°)[4]. The oxirane rings inclined in the opposite direction exhibit comparable dihedral angles (75.2° for $C^3C^4O^1$ and 74.9° for $C^5C^6O^2$).

The influence of the "unsaturated character" of the three-membered ring on the bond length warrants attention: The C^1—C^6, C^2—C^3, and C^4—C^5 bonds (av. 1.480 Å) are significantly shorter than sp^3-sp^3 single bonds (1.54 Å), and close to sp^2-sp^2 single bonds (1.48 Å). This would indicate that multi-conjugated interactions occur between three-membered rings, as assumed between cyclopropane rings and double bonds[3–5].

A planar six-membered ring results in expansion of the "intracyclic" bond angles (120°), thus leading to a tilting

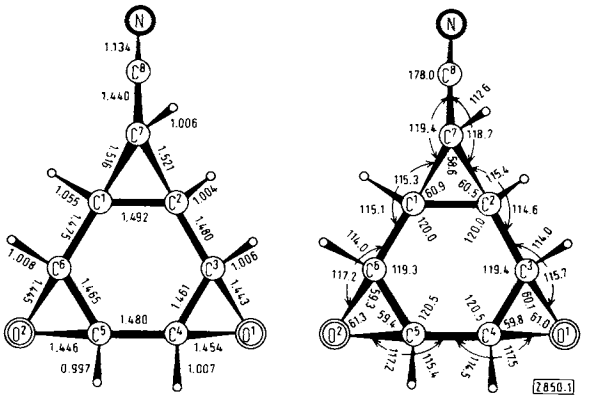


Fig. 1. Molecular structure of the trishomobenzene derivative *(1)*.—a) bond lengths [Å]; standard deviation: 0.004 for C—C, C—O, and C—N, 0.045 Å for C—H.—b) bond angles [ ]; standard deviation: 0.3 for CCC, COC, and CCN, 2.5 for CCH.

of the C—H bonds attached to this ring towards the plane of the ring (average angle 28°).

These results suggest that the central C_6H_6 skeleton assumes a structure intermediate between cyclohexane with sp^3 carbon atoms and a benzene with sp^2 carbon atoms.

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[2] *(1)*, m. p. 104—105 °C, is obtained by photooxygenation of 7-cyanotropilidene followed by thermolysis of the resulting epidioxy compound: *M. Yagihara*, *T. Asao*, and *Y. Kitahara*, to be published.

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(Dimethylcarbamoyl)lithium from Dimethylformamide and Lithium Diisopropylamide; Synthesis of α-Hydroxy *N,N*-Dimethylcarboxyamides

By *Béla Bánhidai* and *Ulrich Schöllkopf*[*]

Several years ago we reported the preparation of (diethylcarbamoyl)lithium *(2b)* by cleavage of bis(diethylcarbamoyl)mercury *(3)* with butyllithium[1,2]. With carbonyl compounds, *(2b)* affords, after hydrolysis, α-hydroxy *N,N*-diethylcarboxyamides and is thus a reagent that makes it possible to introduce the carbamoyl group into carbonyl compounds[2,3]. The preparation of *(3)* is, however, rather troublesome[4] and not without danger, so we sought a simpler access to reagents of type *(2)*[5].

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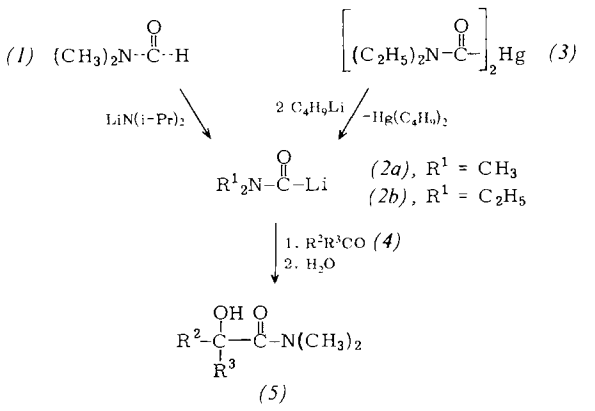

We have now found that α-hydroxy *N,N*-dimethylcarboxyamides *(5)* are obtained, sometimes in good yield, by treating dimethylformamide *(1)* with lithium diisopropylamide in tetrahydrofuran/ether at −78 °C in the presence of carbonyl compounds *(4)* (Table 1). We assume the decisive intermediate to be (dimethylcarbamoyl)lithium *(2a)*[5]. We have not succeeded in metalating *(1)* smoothly and unambiguously by, *e.g.*, butyllithium[6].

Analogously, α-hydroxy *N,N*-dimethylthiocarboxamides [C=S in place of C=O in *(5)* are obtained with *N,N*-dimethylthioformamide *via* (dimethylthiocarbamoyl)lithium [C=S in place of C=O in *(2a)*] and carbonyl compounds.

α-Hydroxy N,N-dimethylcarboxyamides (5)

Dimethylformamide (40 mmol) and a carbonyl compound *(4)* (40 mmol) are dissolved in ether/tetrahydrofuran (4:1; 100 ml) (if necessary in tetrahydrofuran alone). To this solution is added at −78 °C a solution of lithium diisopropylamide that has been prepared *in situ* from diisopropylamine and butyllithium in ether (50 ml) and precooled to −65 C. The whole is stirred for 6 h at −78 °C, allowed to reach room temperature, and hydrolyzed with saturated ammonium chloride solution. The phases are then separated; the organic phase is dried over sodium sulfate and the solvent is removed in a rotary evaporator at water-pump vacuum. The crude amides *(5)* are digested with a little ether, then collected and purified (they are often very clean) either by recrystallization or by column chromatography. In particular, the α-hydroxy dimethylthiocarboxyamides are best purified by chromatography on silica gel with ether/pentane. For very expensive carbonyl compounds [see the synthesis of *(5f)*] a 5- to 10-fold excess of dimethylformamide and lithium diisopropylamide is to be used.

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[4] *U. Schöllkopf* and *F. Gerhart*, Angew. Chem. *78*, 675 (1966); Angew. Chem. internat. Edit. 5, 664 (1966).

[5] Further experiments will show whether compounds *(2)* are better formulated as dialkylamino(lithium oxy)carbenes.

[6] Dimethylformamide is a reagent for formylation of organolithium compounds: cf. *U. Schöllkopf* in *Houben-Weyl:* Methoden der organischen Chemie. Thieme Stuttgart 1969, 4th Edit., Vol. 13/1, p. 187.

Table 1. α-Hydroxy carboxyamides *(5)* prepared.

Cpd.	R^2	R^3	Yield [%]	M.p. [°C]	IR (KBr) νOH	[cm^{-1}] νCO	NMR ($CDCl_3$) (τ values)
(5a)	C_6H_5	H	45	155 [b]	3310	1625	2.65 (s, 5H), 4.80 (s, 1H), 5.28 (s, 1H) [f], 6.98 (s, 3H), 7.24 (s, 3H)
(5b)	C_6H_5	C_6H_5	85	129 [b]	3315	1620	2.67 (s, 10H), 4.12 (br. s, 1H) [f], 7.24 (br. s, 6H)
(5c)	C_6H_5—CH=CH	H	48	89 [c]	3310	1620	2.40–3.00 (m, 5H), 3.28 (d, 1H), 3.91 (q, 1H), 5.12 (d, 1H), 5.7 (br. s, 1H) [f], 7.05 (s, 6H)
(5d)	$(CH_3)_3C$	H	76	66 [d]	3335	1620	5.81 (s, 1H), 6.68 (s, 1H) [f], 6.94 (s, 3H), 7.00 (s, 3H), 9.02 (s, 9H)
(5e)	$-(CH_2)_5-$		62	105 [d]	3340	1620	5.76 (s, 1H) [f], 6.86 (s, 6H), 7.9–8.8 (m, 10H)
(5f)	[a]		72	189 [e]	3500	1605	2.86–3.45 (m, 3 aromat. H), 6.26 (s, CH_3—O—), 6.88 (s, $-NMe_2$), 6.9–8.90 (m, 16H), 7.9 (s, in a multiplet, 1H) [f], 9.02 (s, 18-CH_3)

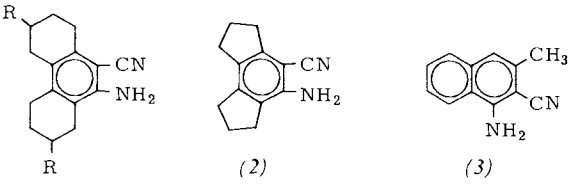
[a] 17-Hydroxy-3-methoxy-*N,N*-dimethyl-1,3,5(10)-estratriene-17-carboxyamide, prepared from the corresponding ketone.
[b] From benzene.
[c] From chloroform.
[d] From cyclohexane.
[e] From cyclohexane/chloroform (5:1).
[f] Proton exchangeable with D_2O.

Elimination of the Nitrile Group from *o*-Amino Nitriles

By *Julian Mirek* and *Janusz Sepiol*[*]

10-Amino-1,2,3,4,5,6,7,8-octahydro-9-phenanthrenecarbonitrile *(1a)* can be prepared in almost quantitative yield by cyclization of (2-cyclohexylidenecyclohexylidene)malonodinitrile by concentrated sulfuric acid at 0 °C[1]. (2-Cyclopentylidenecyclopentylidene)malonodinitrile was recently cyclized thermally (160 °C) to 5-aminohexahydro-*as*-indacene-4-carbonitrile *(2)*[2]. Similarly, (α-methylphenethylidene)malonodinitrile is converted by concentrated sulfuric acid at room temperature into 1-amino-3-methyl-2-naphthonitrile *(3)* in high yield[3].

According to *Jäger*[1] the cyano group of *(1a)* cannot be hydrolyzed because of steric hindrance, and in *(2)*



(1a), R = H *(1b)*, R = CH_3

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and *(3)* it is hydrolyzed only to the amide group and then with difficulty[2,3]. We, however, have found that the *o*-amino nitriles *(1a)*, *(1b)*, *(2)*, and *(3)* are converted into the amines by heating (200 °C) for several hours with alcoholic sodium hydroxide in an autoclave. This "denitrilation" probably occurs by way of the *o*-amino carboxylic acid (or its anion), which is unstable under the reaction conditions (Table 1).

Table 1. Denitrilation of *(1a)*, *(1b)*, *(2)*, and *(3)*.

Nitrile	Reaction time [h]	Amine Yield [%]	M.p. [°C]
(1a)	8	74	65—66
(1b)	8	71	76—77
(2)	7	46	45—46
(3)	6	82	50—51 [a]

[a] M.p. 51—52 °C [4].

General experimental procedure:

The *o*-amino nitrile (5 g) and sodium hydroxide (5 g) are heated in ethanol (80 ml) in an autoclave for some hours at 200 °C. The alcoholic solution, which contains ammonia, is filtered from sodium carbonate, the filtrate is diluted with water (60 ml), and the ethanol is distilled off. The precipitate, at first oily, crystallizes on cooling. The amine that crystallizes from the solution is purified by sublimation in a vacuum and subsequent recrystallization from light petroleum.

The structures of the new amines from *(1a)*, *(1b)*, and *(2)* are proved by analytical and spectroscopic studies.

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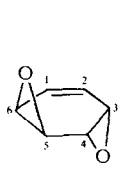
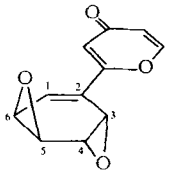
anti-Benzene Dioxide

By *Emanuel Vogel*, *Hans-Josef Altenbach*, and *Erich Schmidbauer*[*]

Benzene is theoretically capable of forming five oxides—benzene oxide[1], *syn*-benzene dioxide[2], *anti*-benzene dioxide[3,4], *syn*-benzene trioxide[5,6], and *anti*-benzene trioxide[5,7,8]—of which all except the *anti*-benzene dioxide *(1)* have been prepared within the last few years. An important stimulus for attempting the synthesis of the as yet unknown *(1)* was provided by the discovery of an antibiotic with the *anti*-benzene dioxide structure *(2)* reported very recently by *Borders et al.*[9]. Preparation of *(1)* appeared all the more desirable since our investigations of *syn*-benzene dioxide *(5)* have cast doubts upon the configuration tentatively assigned to the natural product[2].



(1)



(2)

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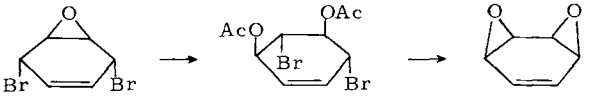
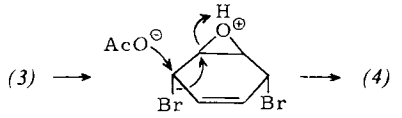
The relatively easily accessible dibromo epoxides *(3)* and *(7)* provided starting materials for the preparation of the *syn*- and *anti*-benzene dioxides, respectively.

As already reported[2b], reaction of *(3)* with acetic anhydride and sulfuric acid[10] leads to a diacetate that affords the desired *syn*-benzene dioxide *(5)* on treatment with methanolic potassium hydroxide. The structure of the diacetate was not clarified at that time, but it was apparent that it could not be the *cis*-1,2-diacetate (3*t*,6*t*-dibromo-1*r*,2*c*-diacetoxy-4-cyclohexene[11]) expected from the projected synthesis of *(5)*.



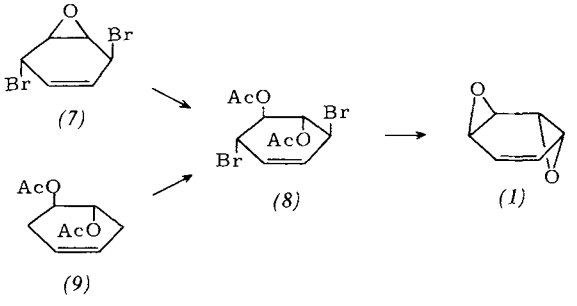
(3) *(4)* *(5)*

The intermediate diacetate has now been recognized as the *cis*-1,3-diacetate *(4)*. The structure *(4)* is indicated in particular by the chemical finding that the diacetate is converted by catalytic hydrogenation over $Pd/BaSO_4$ in ethanol into 2*t*-bromo-1*r*,3*c*-diacetoxycyclohexane[11] (m.p. 79—80 °C), from which *cis*-1,3-diacetoxycyclohexane is obtained on reductive elimination of bromine with Raney nickel in ethanol[12]. *(4)* corresponds in configuration and with great certainty also in conformation to conduritol B (5-cyclohexene-1*r*,2*t*,3*c*,4*t*-tetrol), which is known from NMR studies[13] to assume the energetically favorable half-chair conformation with four equatorial substituents. In actual fact, an NMR analysis of *(4)*[14] carried out on the basis of a half-chair conformation by double resonance and partial INDOR technique provided coupling constants that accord excellently with those for conduritol B. The formation of *(4)* becomes intelligible if one assumes that a neighboring group effect[15] comes into play on opening of the epoxide ring, as indicated in *(6)*.



(3) *(4)* *(6)*

The synthesis of *anti*-benzene dioxide *(1)* was realized starting from the dibromo epoxide *(7)*.

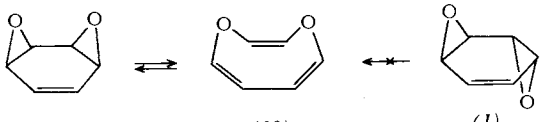


(7) *(8)* *(1)* *(9)*

When *(7)* was treated with acetic anhydride and sulfuric acid at room temperature, the main product was a *cis*-1,3-diacetate (m.p. 105 °C) formed analogously to *(4)*, but there was also obtained a small amount (1 %) of the *trans*-1,2-diacetate *(8)* [m.p. 175—176 °C; NMR ($CDCl_3$): singlet at $\tau = 4.1$ (2 olefinic H), AA'BB' system at $\tau = 4.6$ and 5.25 (4 tertiary H), and singlet at $\tau = 7.9$ (6 acetate-H)]. An alternative route to *(8)* is provided by the reaction of *trans*-1,2-diacetoxy-4-cyclohexene *(9)* with *N*-bromosuccinimide in carbon tetrachloride, which yields *(8)* in admixture with isomers from which it can be separated by fractional crystallization from ether[16].

NMR spectroscopic comparison with the conduritols, as well as catalytic hydrogenation, also proved useful for clarification of the structure and stereochemistry of *(8)*. It was shown that the NMR spectrum of the compound was wholly analogous in its splitting pattern to that of conduritol B. 5 % Methanolic potassium hydroxide causes smooth dehydrohalogenation of *(8)* with formation of a non-phenolic substance of composition $C_6H_6O_2$, m.p. 55 °C (from ether), which was identified as *anti*-benzene dioxide *(1)* by means of its spectroscopic and chemical properties.

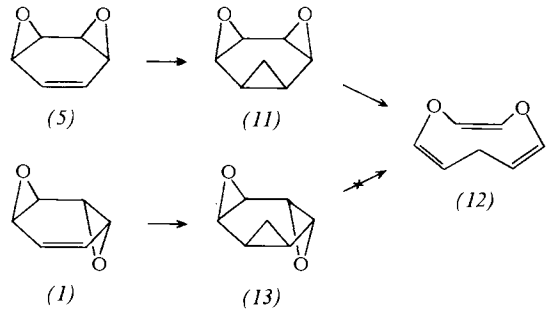
The NMR spectrum (100 MHz, CCl_4) of *(1)* is very similar to that of the *syn*-isomer in that it shows a triplet at $\tau = 3.93$ (1-H, 2-H) and multiplets at $\tau = 6.24$ (4-H, 5-H) and 6.92 (3-H, 6-H). Here too the epoxide protons were assigned on the strength of the observation that the multiplet at higher field was simplified on irradiation at the resonance frequency of the olefinic protons. The simplified multiplet and the multiplet lying downfield then formed an AA'BB' system whose analysis yielded the coupling constants of the epoxide protons ($J_{3,4} = 4.22$, $J_{4,6} = 0.75$, $J_{4,5} = 1.74$, and $J_{3,6} = 0.01$ Hz). The IR spectrum contains pronounced bands in the region 750—950 cm^{-1}, which indicate the presence of epoxide rings. There is no absorption in the UV spectrum above 220 nm. The known *anti*-1,2,3,4-diepoxycyclohexane[17] was formed, as expected, on catalytic hydrogenation of the new benzene dioxide over Pd/C in ethyl acetate.



(5) *(10)* *(1)*

On storage *(1)* suffers relatively rapid decomposition of undefined nature but it is nevertheless remarkably stable thermally: whereas *(5)* equilibrates with 1,4-dioxocin *(10)* even at 50 °C, *(1)* does not isomerize even at 150 °C (in benzene).

The synthesis of *anti*-benzene dioxide *(1)* allows the configuration assigned to the antibiotic *(2)* to be tested. Tools for this are provided not only by the thermal behavior but also by the size of the vicinal coupling $J_{4,5}$ of the epoxide protons 4-H, 5-H. If the Karplus equation is valid[18], $J_{4,5}$ should be 8.5 Hz for the *syn*-configuration and 3 Hz for the *anti*-configuration, since the epoxide protons exhibit dihedral angles of 0 and 50°, respectively. Actually, however, $J_{4,5}$ for *syn*- and *anti*-benzene dioxide are found to be 2.83 and 1.74, respectively. This diminution of the vicinal couplings with retention of the relation $J_{syn} > J_{anti}$ corresponds to observations by *Tori et al.*[19] that in the 1,2-epoxycyclohexane system $J_{vicinal}$ between an epoxide proton and the proton on the neighboring carbon



(5) *(11)* *(12)* *(1)* *(13)*

atom is appreciably smaller, for dihedral angles between 0 and *ca.* 50°, than would be expected from the Karplus equation. In the light of this finding the coupling $J_{4,5}$ of 2.8 found for *(2)* can hardly be interpreted except on the assumption that, contrary to the previous assignment, the antibiotic is a derivative of *syn*-benzene dioxide.

The two benzene dioxides *(5)* and *(1)* undergo interesting reactions. For example, if *(5)* is treated with ethereal diazomethane at 0 °C, a sterically pure pyrazoline (m.p. 67—70 °C, dec.) is formed relatively rapidly. On irradiation with a high-pressure Hg lamp this affords a dioxatrishomobenzene [m.p. 83—84 °C; NMR ($CDCl_3$): multiplets at $\tau = 6.6$ (epoxide-H), 8.65—9.0 (tertiary cyclopropane-H), 9.1—9.4 (*exo*-CH_2-cyclopropane-H), and 9.5—9.75 (*endo*-CH_2-cyclopropane-H)], which isomerizes above 150 °C by a $[\sigma 2_s + \sigma 2_s + \sigma 2_s]$ cycloreversion that affords a quantitative yield of all-*cis*-1,4-dioxa-2,5,8-cyclononatriene *(12)* [b.p. 53 °C/11 torr; $n_D^{20} = 1.4962$; NMR ($CDCl_3$): doublet at $\tau = 3.8$ (5-H, 9-H), singlet at $\tau = 4.2$ (2-H, 3-H), quartet at $\tau = 5.1$ (6-H, 8-H), and triplet at $\tau = 7.0$ (2 7-H)]. Following the rearrangement of the dioxatrishomobenzene in the temperature range 140.5—155.3 °C kinetically gave the values $E_a = 35.5 \pm 1.5$ kcal/mol and $A = 2.2 \times 10^{14}$ for the activation parameters; the relatively low activation energy for this cycloreversion provides subsequent proof that the dioxatrishomobenzene is the all-*syn*-isomer *(11)* and that the addition of diazomethane to *(5)* occurs from the side of the epoxide rings.

From *(1)* one can obtain analogously the *anti*-dioxatrishomobenzene *(13)* [b.p. 63—64 °C/0.7 torr; $n_D^{20} = 1.5013$; NMR ($CDCl_3$): multiplets at $\tau = 6.4$—6.9 (epoxide-H), 8.5—8.95 (tertiary cyclopropane-H), and 9.0—9.4 (CH_2-cyclopropane-H)], which, unlike *(11)*, remains unchanged when heated at 150 °C.

(12) is of interest because it may be possible, by hydride abstraction, to convert it into a monocyclic 10π carbenium ion containing two oxygen atoms, and attempts to generate this ion are in progress.

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[3] The essential properties of *(1)* have already been communicated by us [2b], but the mode of formation of the compound was not clear at that time.

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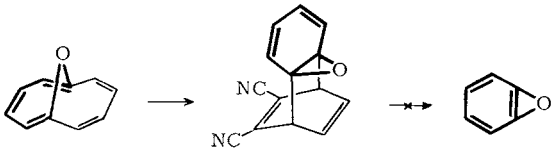
Arene Oxide-Arene Oxide Rearrangements

By *Frank-Gerrit Klärner* and *Emanuel Vogel*[*]

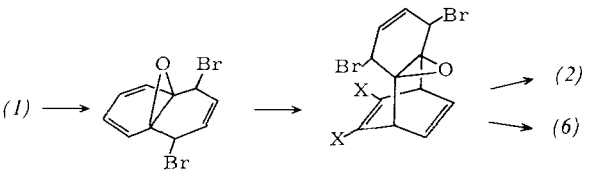
In the course of mechanistic studies of the NIH shift[1] *Bruice* and *Jerina*[2] recently subjected the isomerization of indane 3a,7a-oxide, described by us[3], to detailed kinetic analysis. These authors found that in this reaction an arene oxide-arene oxide rearrangement—a so-called oxygen walk—competes with the known dienone-phenol rearrangement. In an entirely different context, namely while trying to synthesize aryne oxide (3) (benzoxirene), we have been able to observe an arene oxide-arene oxide rearrangement directly.



(1) (2) (3)

Aryne oxide (3) should be accessible by a Diels-Alder reaction of 1,6-oxido[10]annulene (1) with dicyanoacetylene and subsequent Alder-Rickert cleavage of the expected adduct (2)[4].

Realization of the projected synthesis met with difficulties even at the first stage, since (1) did not undergo a Diels-Alder reaction either with dicyanoacetylene or with other dienophiles. An attempt was therefore made to obtain (2) circuitously, through the known dibromo adduct (4)[5] of (1). (4) added one mol of dicyanoacetylene or dimethyl acetylenedicarboxylate already at room temperature forming the adducts (5a) and (5b), respectively (m.p. ≈ 190 °C dec. for both adducts). When (5a) was then treated with sodium iodide in acetone at room temperature, the desired (2) [m.p. 122 °C (from ethyl acetate); 53% yield] was formed as expected; surprisingly, however, (2) was accompanied by an isomer [m.p. 132 °C (from ethyl acetate)] formed in 25% yield[6]. In the dehalogenation of (5b) the only product isolated (70% yield) was a substance [m.p. 91—92 °C (from ether)] corresponding to the above isomer.



(4) (5a), X = CN
[(5b), X = $COOCH_3$]

Proof of the structure of (2) rests on spectral findings. The NMR spectrum ($CDCl_3$), for which no temperature-dependence is observed, consists only of a singlet at $\tau = 3.57$ (protons of the conjugated double bonds) and an A_2X_2 system at $\tau = 3.61$ (protons of the isolated double bond) and 5.70 (bridgehead protons), corresponding to the symmetry of (2) and of its oxepin valence tautomer (7). That the product is the arene oxide valence tautomer (2) follows from the singlet at $\tau = 3.57$ which is to be regarded as a degenerate A_2B_2 system, as singlets at similar positions have been observed for arene oxide protons of (4) and tetralin 9,10-oxide[5]. Also, the UV spectrum with a maximum at 250 nm ($\varepsilon = 7270$) in dioxane can be accommodated only by the arene oxide form[3]. It is the bracket effect of the 1,6-bridge that must be held responsible for suppression of the arene oxide-oxepin equilibration of (2), as in the cases of (4) and tetralin 9,10-oxide.

According to the IR spectrum the isomeric dehalogenation product of m.p. 132 °C is neither a phenol nor a ketone. IR bands at 805, 865, and 880 cm^{-1}, and in particular a UV maximum at 253 nm ($\varepsilon = 8080$) in dioxane, strongly suggest that the compound in question is a fixed arene oxide, as is true of (2). On the basis of this finding, the NMR spectrum (100 MHz; $CDCl_3$) of this compound can be interpreted unambiguously in terms of structure (6). The assignments, made by decoupling experiments, are as follows: multiplet at $\tau = 3.30$ (protons of the isolated double bond), multiplet at $\tau = 3.55$—3.83 (protons of the conjugated double bonds)[7], quartets at $\tau = 5.25$ and 6.15 (bridgehead protons), and quartet at $\tau = 5.70$ (epoxide-proton). The NMR spectrum of (6) remains unchanged up to 120 °C, which is the limit of stability of the compound, whence it follows that the arene oxide is not in equilibrium with any significant concentration of its oxepin valence tautomer (8). There is as yet no indication of a possible isomerization of (6) by inversion of the epoxide ring in which an intermediate formation of (8) would become manifest. Above 120 °C (6) rearranges to the expected phenol (m.p. 177 °C dec.; OH group in α-position to the annelated bicyclic system), which is obtained also by treating (2) or (6) with a Lewis acid.

At this point it must be noted, however, that the spectra do not permit unambiguous differentiation of (6) from its stereoisomer with the inverted epoxide ring. In the unlikely event that (6) should undergo an essentially irreversible inversion of the epoxide ring already under the conditions of its formation it would be necessary to revise the configuration assigned to the present arene oxide.

The reason why the arene oxide-oxepin equilibrium is not observed with (6) is clearly to be sought in the fact that the oxepin valence tautomer (8) contains a relatively strained barrelene partial structure. According to

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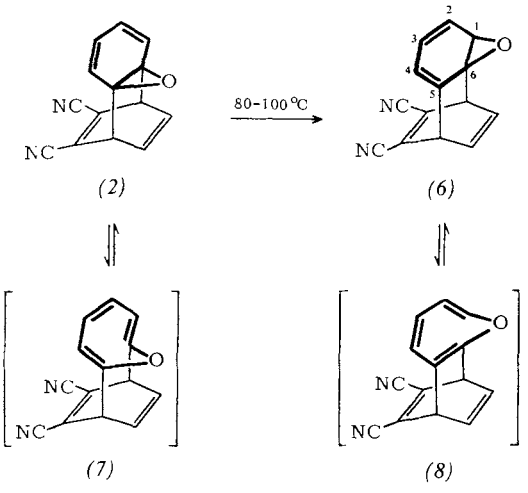
Turner[8], the heat of hydrogenation of the first double bond of barrelene is 9 kcal/mol greater than for the remaining two double bonds, a value that is to be regarded as a measure of the destabilization of this molecule. Beyond doubt, therefore, the "dihydrobarrelene" *(6)* is lower in energy than *(8)* by several kcal/mol even though it contains an exocyclic double bond that must increase the strain[9]. Such an energy difference is more than enough to freeze in completely the arene oxide form *(6)*.



Contrary to expectation, thermolysis of *(2)* does not lead to liberation of the C_6H_4O unit *(3)* by Alder-Rickert cleavage. Instead of the desired cleavage process a quantitative arene oxide-arene oxide rearrangement takes place already at 80—100 °C, yielding *(6)*. Following this rearrangement kinetically (by NMR spectroscopy) in acetone gave a half-reaction time of 343 min at 80 °C; the activation parameters in the same solvent measured between 80 and 110 C are $E_a = 28.2 \pm 0.8$ kcal/mol and $A = 10^{13.0}$. The rate of the reaction does not exhibit a significant solvent dependence; the factor found for $k_{CD_3CN}/k_{C_6D_6}$ was 3, which accords with conditions in Diels-Alder reactions[10]. This last finding eliminates the possibility that a dipolar intermediate is involved. The isomerization of *(2)* to *(6)* constituting a suprafacial 1,5-sigmatropic shift is symmetry-allowed[11]. The reaction may be considered as a pendant to the Berson-Willcott rearrangement[12] of cycloheptatriene-norcaradiene systems. However, in the present case the stereochemical consequence of a concerted reaction course, namely retention of configuration of the migrating group, cannot be determined experimentally[13].

An arene oxide-arene oxide rearrangement, albeit in masked form, was already encountered by us previously in the thermolysis of 1,6-oxido[10]annulene *(1)*, which in cyclohexane at 180 C (half-reaction time *ca.* 13 h) leads almost exclusively to 1-benzoxepin[14]. We believe that a thermal arene oxide-arene oxide rearrangement would be realizable with benzene oxide itself if it became possible to suppress the catalytically-induced aromatization leading to phenol, and attempts are in progress to uncover such a rearrangement (in this case degenerate) by isotopic labeling.

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German version: Angew. Chem. 85, 864 (1973)

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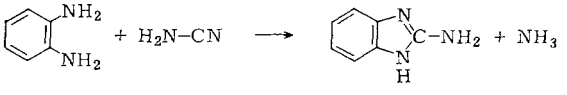
[14] Unpublished experiments.

A New, Simple Synthesis of 2-Aminobenzimidazole

By *Stefan Weiss, Horst Michaud, Horst Prietzel,* and *Helmut Krommer*[*]

2-Aminobenzimidazole *(1)* is an important parent substance, *e.g.* for pesticides. Although it can be obtained by ring closure of *o*-phenylenediamine with cyanogen bromide[1], this process is unsuitable for industrial work. We have been able to prepare *(1)* in almost quantitative yield and in excellent purity by treating *o*-phenylenediamine with cyanamide, which is readily available on an industrial scale[2].



(1)

Experimental:

A 50% aqueous solution of cyanamide (23.1 g, 0.55 mol) is added dropwise during 20 min to a boiling solution of *o*-phenylenediamine (54.1 g, 0.50 mol) in concentrated hydrochloric acid (0.50 mol), and the mixture is kept at 100 C for 1 h. 50% sodium hydroxide solution (0.52 mol) is then added and the whole is heated under reflux until evolution of ammonia is almost complete. The precipitate of 2-aminobenzimidazole *(1)* is isolated, washed free from chloride, and dried in a vacuum; it forms pale brown leaflets (61.3 g, 92%), m.p. 228—229 C.

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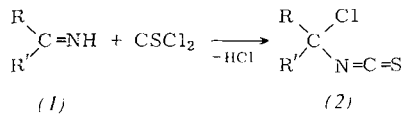
α-Chloroalkyl and α-Alkenyl Isothiocyanates

By *W. I. Gorbatenko, W. A. Bondar,* and *L. I. Samaraj*[*]

We have found[1] that ketimines *(1)* not containing a β-hydrogen atom react with thiophosgene (100—110 °C, in toluene) to afford α-chloroalkyl isothiocyanates *(2)* (cf. ref. [2]).

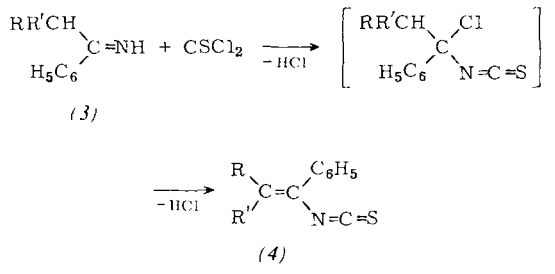


(1) *(2)*

Cpd.	R	R′	Yield [%]	B.p. [°C/torr]	n_D^{20}	d_4^{20}	νNCS (cm^{-1})
(2a)	$C(CH_3)_3$	$C(CH_3)_3$	39	115/15	1.5230	1.0648	2070
(2b)	$C(CH_3)_3$	C_6H_5	50	98/0.06	1.5778	1.1378	2040
(2c)	C_6H_5	C_6H_5	82	135/0.07	1.6380	1.2314	2020
(2d)	α-$C_{10}H_7$	α-$C_{10}H_7$	81	[a]	--	—	2010

[a] M.p. 104—105 °C.

However, α-alkenyl isothiocyanates *(4)* are obtained from the ketimines *(3)* and thiophosgene under the same conditions; α-chloroalkyl isothiocyanates are probably formed as intermediates.



(3) *(4)*

Cpd.	R	R′	Yield [%]	B.p. [°C/torr]	n_D^{20}	d_4^{20}	νNCS [cm^{-1}]
(4a)	CH_3	CH_3	73	65/0.1	1.6120	1.0820	2120
(4b)	H	n-C_3H_7	62	92/0.1	1.6000	1.0660	2100
(4c)	H	i-C_3H_7	77	85/0.1	1.6018	1.0421	2100

The compounds *(2)* and *(4)* are very reactive. As reactants we have so far used chlorine, water, alcohols, amines, sodium azide, phosphites, and dithiophosphoric esters. The IR spectra accord with the structures assigned.

Experimental:

The ketimine *(1)* or *(3)* (0.05 mol) in toluene (50 ml) is added dropwise to a stirred and ice-cooled solution of thiophosgene (0.05 mol) in dry toluene (50 ml). A precipitate separates. The mixture is boiled for 2—3 h; if the precipitate does not redissolve it is filtered off. The solvent is removed in a vacuum and the *(2)* or *(4)* is distilled.

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Preparation of Carbonyl Bis(diphenylphosphide)

By *Hermann J. Becher* and *Ernst Langer*[*]

Use of diphenyl(trimethylsilyl)phosphane *(1)* as reagent for introduction of the $-P(C_6H_5)_2$ group makes it possible to obtain bis(diphenylphosphides) under mild conditions even from dicarboxylic acids such as oxalic and phthalic acid, although in these cases acyl phosphides cannot be prepared from acyl chlorides and alkali-metal diorganylphosphides[1]. Since the latter method also failed in attempts to prepare the hitherto unknown bis(organylphosphides) of carbonic acid[2], it seemed to us promising to treat *(1)* with phosgene as a continuation of our previous work[1]. Carbonyl bis(diphenylphosphide) *(2)*, which was to be expected from the reaction:

$$\underset{}{COCl_2} + \underset{(1)}{2(CH_3)_3SiP(C_6H_5)_2} \rightarrow \underset{(2)}{CO[P(C_6H_5)_2]_2} + 2(CH_3)_3SiCl$$

was indeed isolated as a yellow solid when the reactants were mixed in ether at −110 °C. Similar experiments at −60 °C or higher temperatures were unsuccessful; under these conditions we observed evolution of CO, as did also *Issleib et al.* in their experiments with alkali-metal diorganylphosphides[2]; further, we were able to prove the formation of tetraphenyldiphosphane in the solution.

When the solid product *(2)* is separated from the reaction solution at low temperature it is then fairly stable at room temperature if oxygen is excluded: in the presence of oxygen, vigorous oxidation occurs after a short delay, and the yellow color becomes paler. If heated, the compound decomposes even if air is excluded.

Elemental analyses for C, H, and P gave correct values. The IR spectrum of *(2)* was determined for a KBr disk in an evacuated low-temperature cell at −196 °C and showed, along with numerous bands of the $-P(C_6H_5)_2$ group, a band at 1602 cm^{-1} whose intensity decreased rapidly when the sample was warmed to room temperature and air was admitted to the cell; the yellow color of the sample disappeared simultaneously. This band is thus to be regarded as νCO of *(2)*, being considerably lower than for other carbonyl compounds; a similar effect was observed by *Brook et al.* for $CO[Si(C_6H_5)_2]_2$ and $CO[Ge(C_6H_5)_3]_2$[3]. These compounds resemble *(2)* also in their low stability.

Experimental:

A solution of *(1)* (7.4 g, 0.029 mol) in diethyl ether (20 ml) is added dropwise to a stirred solution of $COCl_2$ (1.42 g, 0.014 mol) in diethyl ether (35 ml) at −100 °C under nitrogen. The mixture at once becomes yellow and after

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[1] *H. J. Becher, D. Fenske,* and *E. Langer,* Chem. Ber. *106*, 177 (1973).

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[3] *A. G. Brook* and *G. I. D. Peddle,* J. Organometal. Chem. *5*, 106 (1966).

a short time a yellow precipitate separates; this is collected on a cooled frit with exclusion of oxygen. The yield of *(2)* is *ca.* 40%.

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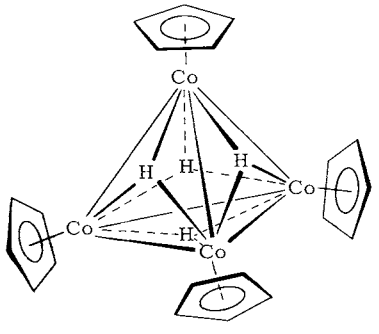
Tetrameric η-Cyclopentadienylcobalt Hydride — A New Type of Four-center Cluster with μ_3-Hydrido Bridges[**]

By *Jörn Müller* and *Horst Dorner*[*]

Relatively little is known about reactions of coordinated nitric oxide although theoretically a variety of such reactions is possible. Our earlier successful experiments with addition of carbanions to the N atom of a nitrosyl ligand[1] induced us to study the possibility of a similar hydride addition. The reduction of an NO to an NH_2 ligand has already been described for the case of reaction of cyclopentadienyldinitrosylchromium chloride with $NaBH_4$[2]. We report here the quite different course of reduction of an η-cyclopentadienylnitrosylmetal complex by a hydride reagent.

If the dimeric cyclopentadienylnitrosylcobalt[3], $[C_5H_5CoNO]_2$ *(1)*, is treated in tetrahydrofuran at 20 C under argon with $LiAlH_4$ in presence of $AlCl_3$, evolution of gas (H_2 and N_2) and change of color from dark olive to dark brown occur. After hydrolysis, a complex of composition $C_{20}H_{24}Co_4$, which forms dark violet shiny crystals, readily soluble in pentane, benzene or ether, can be isolated in 43% yield; when heated under N_2 at 300 C this neither melts nor undergoes any other change. In the solid state the compound is stable in air, but in solution it decomposes on access of air. Because of its properties and spectroscopic data we assign structure *(2)* to the complex.



(2)

The dipole moment of only 0.69 ± 0.1 D, measured in benzene—the true value is probably lower rather than higher—indicates a very symmetrical structure for the compound. The base peak in the mass spectrum is formed by the molecular ion $C_{20}H_{24}Co_4^+$ (*m/e* 500); except for the ions produced by loss of H therefrom, the intensities of other fragments are relatively low. The IR spectrum (KBr) shows the occurrence of equivalent, π-bonded, symmetrical cyclopentadienyl ligands by the following absorptions (the corresponding bands for cobaltocene are shown in parentheses for comparison): 3090 (3060), 1416 (1412), 1103 (1103), 998 (993), 817 (859) and 785 (777) cm^{-1}. Correspondingly, in the ^{1}H-NMR spectrum ([D_8]-tetrahydrofuran) there is one singlet for the five-membered ring protons at $\tau = 5.08$. The existence of bridging hydride ligands follows on the one hand from the metal-hydride vibration at only 950 cm^{-1} (expected region 1100 ± 300 cm^{-1}[4]), which characteristically appears as a broad band in the IR spectrum (a shoulder at 890 cm^{-1} and a further weaker band at 1052 cm^{-1} could also be assigned to Co—H vibrations, but proof of this through the deuteriated compound is not yet available); secondly, a signal at the unusually high τ value of 33.06 is observed in the ^{1}H-NMR spectrum. This and the high symmetry of the complex are best brought into accord with occurrence of μ_3-hydrido bridges. The diamagnetism is also in agreement with the proposed structure in which the Co atoms have noble-gas configurations and are each involved in three metal-metal bonds.

The complex *(2)* is the first organometallic four-center cluster without carbonyl ligands. The primary step in its formation is probably nucleophilic attack by hydride on the nitrosyl-nitrogen of *(1)*. The catalytic role of the aluminum chloride in the redox reaction probably consists of activation of the NO ligand by coordinative interaction with its O atom. Analogous interactions have been observed with carbonyl-metal complexes[5].

Experimental:

All operations must be carried out under argon or nitrogen. A solution of *(1)* (6.16 g, 20 mmol) and $AlCl_3$ (5.3 g) in THF (200 ml) is added dropwise to a stirred solution of $LiAlH_4$ (1.6 g, 42 mmol) and $AlCl_3$ (5.3 g) in THF (200 ml), whereupon gas is evolved (*ca.* 1.4 l). After 24 h the solvent is removed, the residue is stirred vigorously with benzene and water, and the benzene phase is washed with $NaHCO_3$ solution and dried over Na_2SO_4. Removal of the benzene affords almost pure *(2)* (2.15 g, 43%). For further purification the product is dissolved in pentane/benzene (1 : 1) and filtered from a layer (10 cm long, 3 cm wide) of Al_2O_3 (Woelm, 7% of water); it may then be recrystallized from pentane/THF (4 : 1) with severe cooling.

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Concerted Fragmentation of a 1,6-Diradical on Thermolysis of 1,2-Dioxanes[1][***]

By *Waldemar Adam* and *James Sanabia*[*]

1,2-Dioxanes such as the tetramethyl derivative *(1a)*[2] should be potential precursors of the 1,6-diradical *(2a)* or the 1,4-diradical *(3a)* provided that the concerted three-

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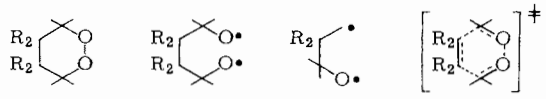
fold fragmentation of *(1a)* into acetone and ethylene by way of the activated complex *(4a)* does not predominate[3]. In order to learn about the chemical fate of such diradicals we have studied the thermolysis and photolysis of *(1)*[4].



(1) *(2)* *(3)* *(4)*

(a), R = H; *(b)*, R = D

When *(1a)* is heated in benzene solution at 200 °C, it is fragmented quantitatively into acetone and ethylene. 2,2-Dimethyloxetane, the cyclization product of the 1,4-diradical *(3a)*, could not be detected even in traces, although control experiments showed that it is stable under the conditions of thermolysis of *(1a)*.

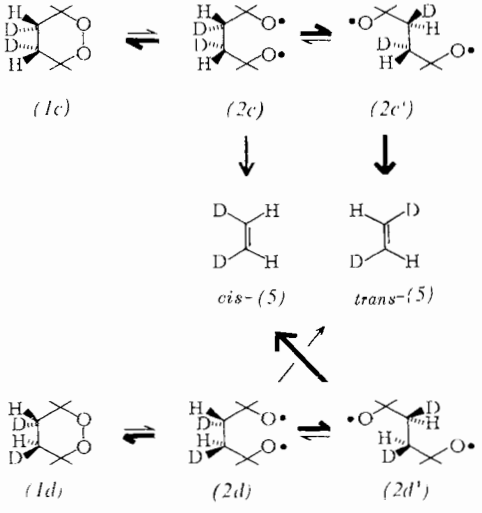
The acetone and ethylene could have been formed, at least in principle, from the 1,6-diradical *(2a)*, from the 1,4-diradical *(3a)* or by the concerted fragmentation pictured in *(4a)*. To clarify the mechanism we have measured 1. the activation parameters, 2. the secondary isotope effect and 3. the stereochemistry of the olefin formation on thermolysis of *(1)*:

1. $\Delta H^{\neq} = 32 \pm 1$ kcal/mol, $\Delta S^{\neq} = -12.6 \pm 1$ cal deg^{-1} mol^{-1}, $\Delta G^{\neq}$ (500 °K) = 38.3 ± 1 kcal/mol for *(1a)*.

2. $k_H/k_D = 1.03 \pm 0.03$, determined for *(1a)* and *(1b)*.

3. 70 ± 2% inversion of the ethylenes *(5)* on thermolysis of *(1c)* and *(1d)*, determined by IR spectroscopy from the ratio of *cis-(5)* to *trans-(5)*. Control experiments showed that *cis-(5)* and *trans-(5)* do not isomerize under the reaction conditions. [Photolysis of *(1c)* and *(1d)* in benzene at 300 nm affords 50% each of *cis-(5)* and *trans-(5)* in both cases; the two ethylenes are photostable at this wavelength.]

The thermolytic results cannot be explained by a concerted three-fold fragmentation of *(1)* by way of *(4)* because in that event the configurations of the olefins should have been quantitatively retained[3] and the secondary isotope effect should have been considerably larger[5]. The results are also not in accord with production of the 1,4-diradical *(3)* because this precursor should have led to complete isomerization of the olefin *(5)* and a considerably larger secondary isotope effect[5]. The 1,6-diradical *(2)* best meets the requirements (see Scheme 1). The stereospecificity of the fragmentation excludes stepwise fission of the 1,6-diradical *(2)* by way of the 1,4-diradical *(3)*.



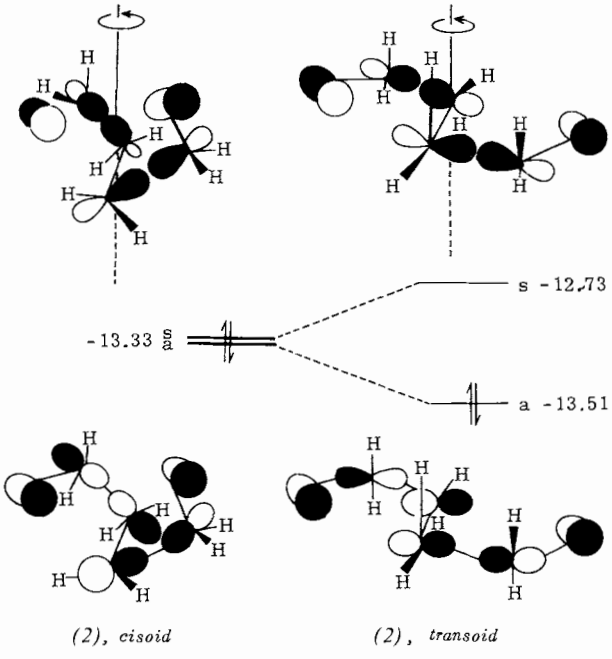
(1c) *(2c)* *(2c')*

cis-(5) *trans-(5)*

(1d) *(2d)* *(2d')*

Scheme 1

The preponderance of inverted ethylene indicates that the activation barrier for concerted double fission to ketone is greater for the cisoid diradicals *(2c)* and *(2d)* than for the transoid diradicals *(2c')* and *(2d')*. EHT calculations[6] showed that for the cisoid 1,6-diradical *(2)* the antisymmetric (a) and the symmetric (s) "diradical" MO's are degenerate, but that for the transoid *(2)* they are split by through-bond coupling[7] [see Scheme 2; there *(2)* is shown with H in place of CH_3]. Now the antisymmetric combination is *ca.* 0.8 eV more stable than the symmetric one; more important, however, is that the antisymmetric "diradical" MO in the transoid conformation is favorably situated for the fragmentation since π-bonded ethylene is formed, whereas the cisoid conformation leads to distorted ethylene. Thus this simple analysis would suggest that concerted fragmentation is more easily undergone by the transoid than by the cisoid conformer.



(2), cisoid *(2), transoid*

Scheme 2

If fragmentation of the 1,6-diradical *(2)* and not homolysis of the peroxide bond determines the rate of reaction, a small isotope effect would be expected since hybridization changes during this fragmentation. In other words, our value of $k_H/k_D = 1.03$ indicates that the energy barrier for concerted fragmentation of the cisoid and transoid 1,6-diradicals *(2)* is higher than that for reclosure to the 1,2-dioxane *(1)*; a similar situation exists for competition between rearrangement and cyclization of the trimethylene diradical[8]. The ready ring opening and recyclization would explain not only the small although not negligible isotope effect but also the negative activation entropy for thermolysis of 1,2-dioxanes *(1)*. For example, 1,2-dioxanes *(1)*, like 1,2-dioxolanes[1], are 10^3 times more stable than *tert*-butyl peroxide. This stabilization is controlled by entropy rather than by enthalpy since for *(1)* $\Delta H^{\neq}$ is *ca.* 6 kcal/mol smaller than for *tert*-butyl peroxide[9]. If reclosure of the 1,6-diradical *(2)* is easier than its fragmentation, then only special conformations of the diradical could decompose to acetone and ethylene and a negative $\Delta S^{\neq}$ value is to be expected. Our kinetic and stereochemical results

thus show that 1,6-diradicals *(2)*, formed by simple homolysis of the peroxide bond of 1,2-dioxane *(1)*, undergo the novel concerted fragmentation described here in preference to the stepwise loss of acetone by way of the 1,4-diradical *(3)*.

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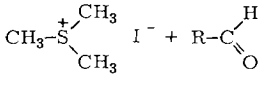
Phase-transfer-catalyzed Production of Sulfur Ylides in an Aqueous System

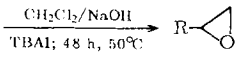
By *Andreas Merz* and *Gottfried Märkl*[*]

There is an increasing number of reports of phase-transfer-catalyzed two-phase reactions[1] in which anionic reactants are transferred from an aqueous to an organic phase by quaternary ammonium salts (benzyltriethylammonium[2] and *n*-hexadecyltrimethylammonium chloride[3] and tetra-*n*-butylammonium iodide[4]). Excellent examples are the cycloadditions[2, 3, 5] and insertion reactions[6] of halocarbenes produced with aqueous sodium hydroxide.

We recently[7] reported on Wittig olefinations by non-stabilized alkylidenetriphenylphosphoranes in the two-phase system dichloromethane/aquesous sodium hydroxide. Our assumption that phase-transfer catalysis is involved in these reactions, brought about by the phosphonium salts, is supported by similar reactions of sulfonium- and oxosulfonium salts described below, which proceed through intermediate sulfonium and oxosulfonium ylides[9]. Like tetraalkylammonium salts containing small alkyl substituents, the trimethylsulfonium ion should not be an effective phase-transfer catalyst; accordingly, trimethylsulfonium iodide *(1)* does not react with benzaldehyde in the two-phase system CH_2Cl_2/NaOH, whereas on addition of 1—5 mol-% of tetrabutylammonium iodide (TBAI) 2-phenyloxirane *(2a)* (b.p. 77 °C/11 torr; $n_D^{20} = 1.5359$[9]) can be isolated in >90% yield.



(1)



(2a), R = C_6H_5
(2b), R = C_6H_5-CH=CH

In spite of the long reaction time of 48 h at 50 °C neither hydrolysis of the sulfonium salt nor a Cannizzaro reaction of the benzaldehyde can be observed.

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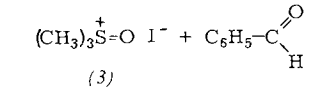
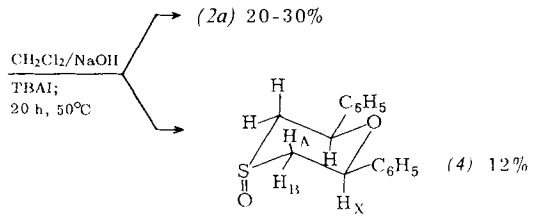
Use of cinnamaldehyde affords equally smoothly an 85% yield of 2-styryloxirane *(2b)*, b.p. 64 C/0.1 torr. ^{1}H-NMR spectrum of *(2b)* in $CDCl_3$ (ppm against internal TMS): aromatic H: 7.20—7.55 (5H); olefinic H: AB portion of an ABX spectrum, centered at 6.37 (2H) ($J_{A-X} = 2$, $J_{B-X} = 8$, $J_{A-B} = 16$ Hz); cyclopropyl-H: 3.30—3.60 m (1H), 2.85—3.15 m (1H), 2.60—2.80 m (1H).

Ketones give only small yields even after prolonged reaction. Acetophenone undergoes 36% reaction in 72 h, and benzophenone 18%, the products again being oxiranes.

The reactions of the trimethyloxosulfonium salt *(3)* are interesting. With benzaldehyde it gives only 20—30% of the oxirane *(2a)*; but this is accompanied by a 12% yield of a colorless, crystalline compound, m.p. 180 °C, which was identified as 2,6-diphenyl-1,4-oxathiane 4-oxide *(4)* by elemental analysis and spectroscopic data.



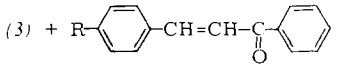
(3)

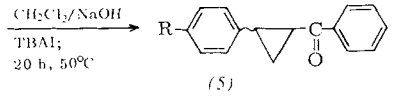


(4) 12%

IR spectrum of *(4)* (KBr disc): νS=O 1025[8], νC—O 1076 cm^{-1}. ^{1}H-NMR spectrum: 7.38 s (10H), AA'BB'X spectrum with δX = 5.60, DXD (2H) ($J_{A-X} = 2$, $J_{B-X} = 10$ Hz), AB potion 2.34—3.20 m (4H) ppm. Mass spectrum: *m/e* = 272 (M^+), 104 (C_6H_5—CH—CH_2^+). Molecular weight (osmometric) = 272 (calc. 272).

(3) reacts remarkably smoothly with α,β-unsaturated aromatic ketones:





(5)

	M.p. [°C]	Yield [%]
R = H [9]	37—43	86
R = CH_3	85—87	78
R = OCH_3	colorless oil	74

Here the same selectivity is evident as was observed by *Corey et al.*[9]: no oxirane is formed, but instead *cis/trans*-mixtures of cyclopropane derivatives.

According to the molecular ratio of the reactants, 1,5-diphenyl-1,4-pentadien-3-one affords mono- or bis-cyclopropane ketones.

2-Phenyloxirane (2a):

Benzaldehyde (10.6 g, 0.1 mol) and TBAI (0.5 g, 1.35 mol) are dissolved in dichloromethane (100 ml) and a layer of 50% aqueous sodium hydroxide is introduced underneath this solution. Trimethylsulfonium iodide (20.4 g, 0.1 mol) is then added and the whole is warmed at 50 C with

vigorous stirring for 48 h, whereupon the originally undissolved sulfonium salt disappears. The reaction mixture is next poured on ice, and the organic phase is separated, washed with water and dried. Distillation affords 11 g (92%) of *(2a)*.

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Phase-transfer-catalyzed Alkylation of Alcohols by Dimethyl Sulfate in an Aqueous System

By *Andreas Merz*[*]

Alcohols cannot be converted into their methyl ethers directly by dimethyl sulfate, and only with difficulty in the form of their alkali-metal salts; exceptions are a few activated alcohols such as propargyl alcohol, benzyl alcohol, cyanohydrins, *etc.*[1,2]. *Sjöberg* and *Sjöberg*[3] describe the methylation of alcohols by dimethyl sulfate in the presence of sodium methylsulfinylmethanide as base.

Prompted by *Herriott* and *Picker*'s study[4] of the phase-transfer-catalyzed hydrolysis of *n*-bromooctane, we here report etherification of alcohols by dimethyl sulfate in a two-phase system by use of the principle of phase-transfer catalysis[5].

On addition of *ca.* 1 mol-% of tetrabutylammonium iodide (TBAI), alcohols react with dimethyl sulfate in two-phase systems involving 50% aqueous sodium hydroxide, to give almost always quantitative yields of their methyl ethers (cf. Table 1).

The organic phase can be either the alcohol itself or a mixture of the alcohol with an inert organic solvent (light petroleum, benzene, ether, dichloromethane). It is not only primary, secondary and tertiary alcohols activated by unsaturated or electron-attracting neighboring groups (examples *1—10*) that react smoothly; saturated primary alcohols do so also (examples *11—15*).

The attacking nucleophile is the alcoholate ion involved in the acid-base equilibrium[4]. Thus, because of their lower acidity secondary alcohols react considerably more sluggishly, and tertiary alcohols do not react at all. In the former case an excess of dimethyl sulfate still gives preparatively useful results (examples *16* and *17*). That steric hindrance plays no part is shown by examples *7* and *10* and also by the smooth formation of methyl neopentyl ether *(15)*.

Table 1. Phase-transfer-catalyzed formation of ethers [a] by the process:

$$ROH + (CH_3)_2SO_4 \xrightarrow{NaOH/TBAI} ROCH_3 + Na[CH_3SO_4] + H_2O$$

	R	Yield [%]	B.p. [°C/torr]	n_D^{20}	Ref.
(1)	$(HC{\equiv}C)_2C(C_4H_9)$ [7]	95	(36)	—	—
(2)	$(HC{\equiv}C)_2C(C_6H_{11})$ [7]	90	56/0.02	1.4789	—
(3)	$(HC{\equiv}C)_2C(C_6H_5)$ [7]	97	56/0.01	1.5308	—
(4)	$C_6H_5{-}CH_2{-}$	92	63/12	1.5028	[1]
(5)	$C_6H_5{-}CH_2{-}CH_2{-}$	90	80/12	1.4991	[1]
(6)	$C_6H_5CH(CH_3){-}$	93	63/12	1.4912	—
(7)	$C_6H_5{-}C(CH_3)_2{-}$	85	85/12	1.5050	—
(8)	$C_6H_5CH{=}CH{-}CH_2{-}$	90	115/12	1.5466	[1]
(9)	$C_6H_5{-}CH(CCl_3){-}$	86	(52)	—	—
(10)	$(C_6H_5)_3C{-}$	80	(81—82)	—	[8]
(11) to *(14)*	$n\text{-}C_nH_{2n+1}$ ($n = 5,6,7,8$)	ca. 90	—	—	—
(15)	$t\text{-}C_4H_9{-}CH_2{-}$	70	80—81/760	1.3725	—
(16)	$CH_3{-}CH(C_3H_7){-}$	60	89—91/760	1.3968	—
(17)	(−)-*p*-Menth-3-yl	54	82—83/12	1.4438[b]	[9]

[a] Ethers not described in the literature were identified unambiguously by IR and NMR spectra.
[b] $[\alpha]_D^{25} = -93°$ (5% in $CHCl_3$).

General procedure:

The two-phase system consisting of (a) a solution of the alcohol to be etherified (0.5 mol) and TBAI (1 g) in light

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petroleum (200 ml) (b. p. 50—70 °C) and (b) 50% aqueous NaOH (1.3 mol) is equilibrated by vigorous stirring for 15—30 min, which causes slight evolution of heat. Dimethyl sulfate (0.6 mol) is then added dropwise, with cooling, during 1 h at a rate such that the temperature does not exceed 45 °C. The whole is next stirred for 2—3 h and, after addition of concentrated aqueous NH_3 (10 ml), for a further 30 min at room temperature. The mixture is finally poured into water and the organic phase is separated, washed with water, dried over Na_2SO_4 and worked up in the usual way.

The experimental results are collected in Table 1. The yields depend to a considerable extent on good mixing; for semimicro batches with magnetic stirring a 1.5-fold excess of dimethylsulfate is therefore recommended.

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Tris(dimethylamino)azacyclobutadiene[**]

By *Günther Seybold, Ulrich Jersak,* and *Rudolf Gompper*[*]

The calculated resonance energies of cyclobutadiene (−18 kcal/mol)[1] and azacyclobutadiene (azete) (−15.5 kcal/mol)[2] demonstrate both the antiaromatic character of these compounds and the stabilizing action of the N atom[3]. In view of the negative resonance energies it is not surprising that attempts to prepare monocyclic aza- and diaza-cyclobutadienes have hitherto failed[4–7]. Even pyrolysis or photolysis of trimethyl- and triphenyl-1,2,3-triazine[8,9] afforded only acetylenes and nitriles. On the contrary, however, gas-phase pyrolysis of 4-phenylbenzo- and 4-phenylnaphtho-1,2,3-triazine led to 2-phenylbenzazete and 2-phenylnaphthazete which are stable at −80 and 20 °C, respectively[10].

According to the push-pull principle[11], introducing amino groups should provide sufficient stabilization for monocyclic aza- and 1,3-diaza-cyclobutadienes to exist. To test this hypothesis we have investigated the photolysis and flash pyrolysis of tris(dimethylamino)-1,2,3-triazine[13]; we obtained this triazine from tris(dimethylamino)cyclopropenylium perchlorate and potassium azide by analogy with known procedures[12].

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[**] Flash Pyrolysis of Organic Compounds, Part 1. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. We thank the Badische Anilin- & Soda-Fabrik AG, Ludwigshafen, for measuring the 220 MHz ^{1}H-NMR spectrum, and Bruker-Physik AG, Karlsruhe, for measuring the ^{13}C-NMR spectrum.

Irradiating an aqueous solution of *(1)* by a 400 W Hanovia lamp completely destroyed this molecule within a short time: only dimethylcyanamide could then be detected in the reaction solution.

Flash pyrolysis of *(1)* was carried out in an electrically heated quartz tube (25 cm long, 1.5 cm in diameter) at 527 °C and 10^{-4} torr. The quartz tube was packed with quartz wool; to avoid secondary reactions, the pyrolyzate was "frozen" at −196 °C immediately after exit from the heating zone. During the pyrolysis the trap became coated with a deep-red deposit. This was dissolved off by methylene chloride at −80 °C. Presence of the triazine *(1)* in the red methylene chloride solution was proved by thin-layer chromatography and that of dimethylcyanamide by gas chromatography. The red color slowly faded at room temperature.

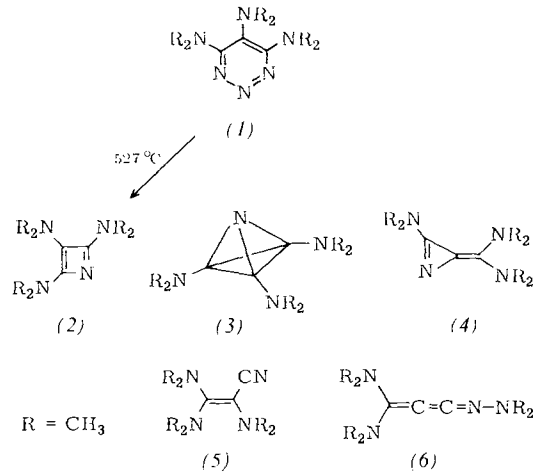
Investigation of the red solution of the pyrolyzate gave the following results:

1. *Mass spectra:* When the direct inlet rod was at a temperature of −25 °C the highest mass was due to an ion with $m/e = 182$. From −10 °C onwards the peak for *(1)* ($m/e = 210$) becomes increasingly stronger with increasing temperature, whilst $m/e = 182$ becomes increasingly weaker. At 100 °C the spectrum corresponds to that of pure triazine *(1)* in which the ion $m/e = 182$ has an intensity of only 1.3%.—The mass spectrum of a pyrolyzate solution that had been kept at room temperature for two days no longer showed the mass peak at $m/e = 182$. From 0 °C onwards new peaks were found in the region between $m/e = 210$ and 340.

We regard the ion of $m/e = 182$ in the spectrum of the fresh pyrolyzate solution as the molecular ion of the red compound, which is evidently relatively easily volatilized and is unstable at room temperature. It is also conceivable that the red product is a thermolabile valence isomer of *(1)* that loses nitrogen already at −25 °C in the mass spectrometer and gives a false mass 182; however, evolution of gas from samples of the reaction product was never observed at room temperature, although release of N_2 during the pyrolysis was recognizable from an increase in pressure from 5×10^{-6} to 10^{-4} torr.

Determination of the molecular weight by high-resolution mass spectrometry gave a value of 182.1486; thence follows a molecular formula $C_9H_{18}N_4$, to which any of the structures *(2)*—*(6)* could be assigned.

Mechanistically, compounds *(2)* and *(3)* are the most likely to be formed from *(1)*. Conversion of *(1)* into *(4)*, *(5)*, or *(6)* requires the assumption that a dimethyl-



amino group migrates in an open-chain intermediate. Compounds *(3)*, *(5)*, and (probably) *(6)* can be excluded because of the red color.

2. *IR spectra:* νC=N of *(1)* 1510 cm^{-1} (CH_2Cl_2), 1520 cm^{-1} (SO_2); νC≡N of $(CH_3)_2N$—CN: 2206 in both solvents. From the red solution new bands appear at 1630 cm^{-1} (CH_2Cl_2) or 1652 cm^{-1} (SO_2). The structures *(3)*, *(4)*, *(5)*, and *(6)* are thus excluded: aminoazirines comparable with *(4)* have a C=N band at 1760 cm^{-1}[14]; from *(5)* one would expect a C≡N band at 2190 cm^{-1} (cf. [15, 16]), and for *(6)*, as a ketene imine derivative[17], a band at 2000 cm^{-1}. Of the structures proposed the only one remaining is thus *(2)* (in 2-alkoxyazetines[18] νC=N has been observed at 1620 cm^{-1}).—The band at 1630 cm^{-1} is not to be found in the IR spectrum of a pyrolyzate solution that has been kept for 2 days at room temperature, is colorless, and no longer shows an ion of $m/e=182$ in the mass spectrum.

3. *UV spectra:* The UV spectrum of a methylene chloride solution of the pyrolyzate, measured at −40 °C, shows an intense absorption maximum at 527 nm with $\varepsilon \approx 20000$ [*(1)*: $\lambda_{max} = 352$ nm]. The disappearance of this maximum at 30 °C follows second order kinetics with a half-life of 56 min (initial absorption 1.100 OD). From theoretical considerations[19] a maximum would be expected for *(2)* at 670 nm; one would predict shorter-wave absorptions for the other structures considered.

4. *NMR spectra:* The ^{1}H-NMR spectra of the pyrolyzate in mixtures of CH_2Cl_2 and CD_2Cl_2 show signals in the range $\delta = 2.5$—3.5 ppm. Singlets at $\delta = 2.75$ and 2.9 ppm can be assigned to the triazine *(1)*, and a singlet at 2.85 ppm to dimethylcyanamide. A 60 MHz ^{1}H-NMR spectrum, measured at −60 °C, shows, besides these signals, two singlets at $\delta = 3.22$ and 2.94 ppm. An intensity ratio of 1:2 can be found from the 220 MHz spectrum. If the sample in the spectrometer is allowed to warm up to room temperature these two singlets disappear simultaneously, being no longer present after *ca.* 12 h, whilst at the same time new signals appear at $\delta = 2.31$ and 3.35 ppm; the solution then has only an extremely faint red color.

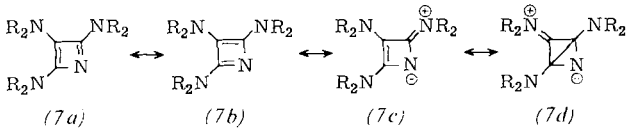
As in the ^{1}H-NMR spectrum, so in the ^{13}C-NMR spectrum two new signals arise, at 138.29 and 128.28 ppm (relative to TMS); these can be assigned to olefinic C atoms.

According to the conditions of the pyrolysis and working up, further signals of lower intensity can be observed in the ^{1}H-NMR spectra of the pyrolyzate; some of them decrease in intensity with increasing temperature.

The following properties can thus be assigned to the red compound in the pyrolyzate solution: molecular weight 182; UV: $\lambda_{max} = 527$ nm ($\varepsilon \approx 20000$); IR: νC=N = 1630 cm^{-1}; ^{1}H-NMR: singlets at $\delta = 3.22$ and 2.94 ppm (1:2).

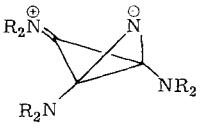
Thence we conclude that tris(dimethylamino)azacyclobutadiene *(2)* is formed on pyrolysis of *(1)*. From the ^{1}H-NMR spectrum the yield can be estimated as approximately 30%.

The relatively high thermal stability and the NMR spectra of the product indicate that *(2)* should be described as the resonance hybrid *(7a)*—*(7d)*, where especial importance attaches to the structure *(7d)*[19]. Provisionally the possibility cannot be excluded that the product has one of the angular structures derived from *(7d)*, *e.g.* *(8)*, although the IR spectrum contraindicates this (cyclopropanimine has C=N bands at 1770 cm^{-1}[20]).



(7a) *(7b)* *(7c)* *(7d)*

R = CH_3



(8)

5. *Chemical behavior:* Experiments in which *(2)* was treated with methyl iodide, tetracyanoethylene, acetylenedicarboxylic ester, phenyl isothiocyanate, tosyl isocyanate, or $Fe(CO)_5$ led to inseparable mixtures of products. The difficulties in working up were partly due to the fact that the triazine *(1)*, which is present in the pyrolyzate in excess of *(2)* (>40%), reacts with electrophiles to give deeply colored, as yet unidentified products[14]. Protonation of *(2)* also seems to take a complicated course.

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The Structure of Triaminoazacyclobutadiene[**]

By *Hans-Ulrich Wagner*[*]

Cyclobutadiene *(1)* is antiaromatic; it can be stabilized by push-pull substitution[1]. Substitution as in compounds of type *(2)* has been found especially advantageous in this respect[2]. Analogously, azacyclobutadiene *(3)*, which

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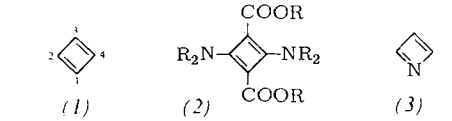
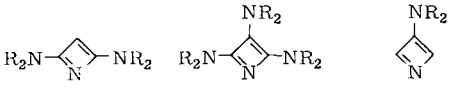
is energetically favored in comparison with *(1)* by introduction of the ring-nitrogen that acts as acceptor, can be further stabilized by two donor groups at positions 2 and 4 [see *(4)*].

From this point of view a third donor group, as in *(5)*, has an unfavorable effect. Introducing a donor group at position 3 relative to the acceptor position, as in *(6)*, however, causes distortion of the ring to a rhombus[3] by increasing the bonding interaction and bringing positions 2 and 4 closer together.



	(1)	*(2)*	*(3)*
p_{13}	0.	−0.16	−0.40
p_{24}	0.	+0.29	+0.46



	(4)	*(5)*	*(6)*
p_{13}	−0.35	−0.34	−0.39
p_{24}	+0.25	+0.35	+0.51

The transannular interaction of atoms at opposite corners of the four-membered ring can certainly no longer be neglected since the distance between them of approximately 2 Å comes in the region of normal bond lengths. The energy change including the effect of the diagonal interaction can be estimated to a first approximation from the bond orders in the HMO scheme (see the values under the formulas)[4].

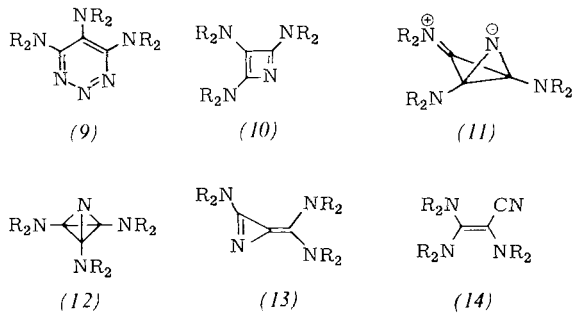
Even in the push-pull-stabilized cyclobutadiene *(2)* closer approach of centers 2 and 4 *and* further separation of centers 1 and 3 should bring an increase in energy. As shown by X-ray structure analysis[5] of *(2)* the measured angles (1—2—3 = 93, 2—3—4 = 87°) and bond lengths (2—4 = 2.00, 1—3 = 2.11 Å) indicate that the four-membered ring is in fact distorted to a rhombus[6].

Although such a distortion does not lead to an energy gain in unsubstituted cyclobutadiene *(1)*[7], considerable stabilization is to be expected for *(3)* in view of the bond orders shown. In the language of resonance theory this distortion favors the polar resonance structure *(7)*.

(7) *(8)*

In *(7)* it can be clearly seen how introducing a donor group at position 3 buttresses the transannular interaction between centers 2 and 4 by stabilizing the positive charge [resonance structure *(8)*]. This effect can also be deduced from the changes in HMO bond orders on going from *(3)* to *(6)* and from *(4)* to *(5)*.

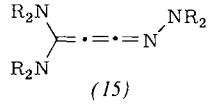
The unstable red product of molecular formula $C_9H_{18}N_4$ obtained on flash pyrolysis of 4,5,6-tris(dimethylamino)-1,2,3-triazine *(9a)*[8] can have one of the structures *(10a)* to *(15a)*. To aid clarification of the structure the electronic spectra to be expected for *(10)* to *(15)* were calculated



(9) *(10)* *(11)*

(12) *(13)* *(14)*

(a), R = CH_3
(b), R = H



(15)

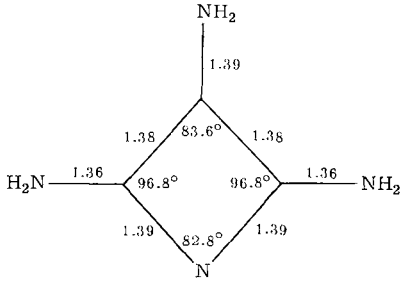
by a CNDO-CI procedure[9] (Table 1); but since it can be assumed that the methyl groups have no appreciable influence on the chromophore of the red compound, the CH_3 groups were replaced by H for the calculations[10].

Table 1. Calculated wavelengths of the longest-wave electronic transitions for various structures $C_3H_6N_4$ ($C_9H_{18}N_4$).

Structure	*(9b)*	*(10b)*	*(11b)*	*(12b)*	*(13b)*	*(14b)*	*(15b)*
λ [nm]	386	670	737	194	393	282	440

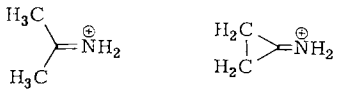
In hexane solution the longest-wave absorption maximum for the triazine *(9a)* that was used as reference molecule appears at 352 nm[11]. The calculated value is shifted to longer wavelength from the experimental value[12]. With this trend in mind it is clear from Table 1 that the red compound in question ($\lambda_{max}^{CH_2Cl_2} = 527$ nm) can have only structure *(10)* or *(11)*.

The structures *(10)* and *(11)* are topologically closely related. On minimization of the energy of *(10)* and *(11)* with respect to *all* the coordinates by the MINDO/2 procedure[13], the most favorable structure with topology close to that of *(10)* is found to be a symmetrical planar four-membered ring with strongly distorted diagonal distances as required by the considerations above (1—3 = 2.07, 2 to 4 = 1.84 Å) but approximately equal lengths for the sides:



Minimization starting from the geometry of the less stable structure *(11)* discloses a tendency towards planarity, giving a planar rhombus *(10)*. A planar structure *(10)* with localized single and double bonds is also energetically less favorable than a symmetrical delocalized structure. Bond fixation of the second order appears to play no part in *(10)*[14].

According to these results the unstable red compound should have structure *(10)*, as assigned also from the physical data[8]. However, the MINDO/2 calculation gives an astonishingly low bond index of 0.962 for the C=$\overset{\oplus}{N}H_2$



(16) (17)

bond of *(11b)*; comparing this value with the bond indices of 1.507 for *(16)* and 1.537 for *(17)* shows that the IR wave number of the C=N stretching vibration of *(11)* is not necessarily so high as for *(16)* and *(17)*.

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Specific Heat and Formation of Kinks in Bimolecular Films of Long-Chain *n*-Alkyl Compounds[**]

By *Gerhard Lagaly*, *Stephan Fitz*, and *Armin Weiss*[*]

Alkyl chains may change their conformation *via* rotation about C—C bonds. Among these isomerizations, the simultaneously occurring transformation of two *trans* bonds (t) into +gauche (g) and −gauche bonds ($\bar{g}$), for example ...ttt... → ...gt$\bar{g}$... or ...ttttt... → ...gttt$\bar{g}$... *etc.*, appears to be important in crystalline, paracrystalline, or partially crystalline compounds. In these cases the two parts of chain beyond the ...gt...$\bar{g}$... conformation remain parallel to each other.

Conformations arising in this way were termed "kinks" by *Pechhold*[1]. They have been discussed as structural elements in polymers[2]; their formation and rearrangement were assigned to definite relaxation regions (cf. *e. g.* Ref.[3]).

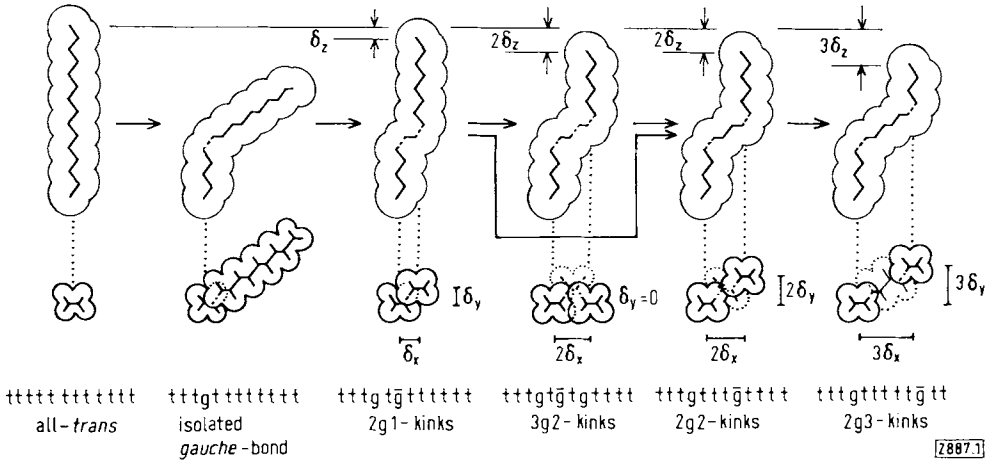

Fig. 1. Conformations of alkyl chains with isolated *gauche* bonds and kinks ($\delta_x = 1.78$, $\delta_y = 1.27$, $\delta_z = 1.27$ Å).

We succeeded in proving the existence of kinks experimentally by measurements of the shortening of the overall chain length upon kink formation[4]. As models we have used bimolecular films of *n*-alkylammonium ions and *n*-alkanols spread out between silicate layers. Kink formation was shown by a stepwise decrease of the film thickness with increasing temperature, measured by X-ray methods. Kink formation is a cooperative process in which the number of kinks per alkyl chain increases by 1 within a relatively small temperature range. For steric reasons, the kinks must be assigned to neighboring chains, so that kink blocks are formed. The cause of kink formation is the increasing thermal energy.

We have now been able to elucidate kink formation by measuring the specific heat of the same models (*e. g. n*-tetradecylammonium-beidellite/*n*-tetradecanol) in an adiabatic calorimeter. A small flask containing the sample was immersed in paraffin as bath fluid, and the specific heat was determined from the change in temperature of the paraffin (measured by an NTC resistance), while a definite amount of heat was supplied by electrical heating. The sensitivity of the calorimeter was better than 20 mcal/h. The experimental results are shown in Fig. 2: curve a)

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[3] If the lengths of the C—N and C—C sides are different, the distorted form corresponds to a kite.

[4] For summands of the first order $\delta E = 2 p_{\mu\nu} \beta_{\mu\nu}$; cf. *E. Heilbronner* and *H. Bock*: Das HMO-Modell und seine Anwendung. Verlag Chemie, Weinheim 1968, p. 146.

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[6] The antibonding interaction in the cyclobutadiene *(2)* is further diminished by the facts that the acceptor substituents do not lie in the plane of the ring and that 2—4 overlap is thus reduced by transhybridization.

[7] In alternant hydrocarbons all bond orders to second nearest neighbors are zero.

[8] *G. Seybold*, *U. Jersak*, and *R. Gompper*, Angew. Chem. *85*, 918 (1973); Angew. Chem. internat. Edit. *12*, 847 (1973).

[9] *R. L. Ellis*, *G. Kuehnlenz*, and *H. H. Jaffé*, Theor. Chim. Acta *26*, 131 (1972); *J. Kroner* and *D. Proch*, Tetrahedron Lett. *1972*, 2537, and literature cited therein.

[10] Standard coordinates were used for all the molecules. It was found that for *(10)* the position of the longest-wave band was not appreciably altered by use of minimum coordinates. As an analytical method the calculations give only *qualitative* information about the spectra to be expected.

[11] *R. Gompper*, *U. Jersak*, and *K. Schönafinger*, personal communication.

[12] An exact analysis of this electronic spectrum is in progress.

[13] MINDO/2: *N. Bodor*, *M. J. S. Dewar*, *A. Harget*, and *E. Haselbach*, J. Amer. Chem. Soc. *92*, 3854 (1970). Minimization by the QCPE program of *A. Komornicki* and *J. W. McIver, Jr.*, Chem. Phys. Lett. *10*, 303 (1971).

[14] The largest eigenvalue calculated by us for the bond-bond polarizability matrix is relatively small. For the theory see: *G. Binsch*, *I. Tamir*, and *R. D. Hill*, J. Amer. Chem. Soc. *91*, 2445 (1969).

shows the decrease in basal spacings between 30 and 90 °C in three sharp steps corresponding to the cooperative introduction of kinks into the alkyl chains; curve b) shows the specific heat per mol of the tetradecanol complex of tetra-

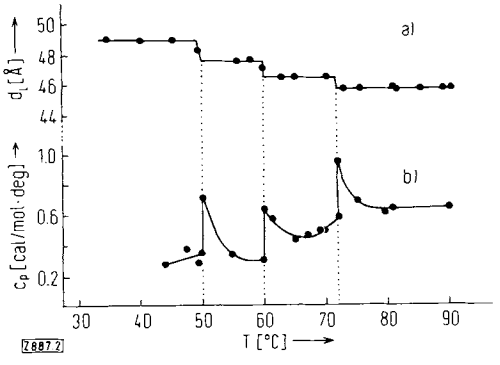

Fig. 2. Change of basal spacing d_L (a) and specific heat c_p (b) of *n*-tetradecylammonium-beidellite/*n*-tetradecanol with temperature (the c_p values are referred to 1 mol of *n*-tetradecylammonium-beidellite).

decylammonium-beidellite. c_p does not change continuously, but shows three distinctly marked transitions similar to λ-transitions occurring at the same temperatures as the steps in the basal spacing.

Table 1. Transition enthalpies and entropies in the system *n*-tetradecylammonium-beidellite/*n*-tetradecanol.

Transition temp. [°C]	ΔH [kcal/mol] [a]	ΔS [cal/deg·mol] [a]
50	0.73	2.3
60	0.72	2.3
72	0.68	2.3

[a] Per mol of beidellite.

From the c_p values the transition enthalpies can be determined by graphical integration and the transition entropies from the c_p/T-values (Table 1). Each set of values is of the same order of magnitude for each transition. Per formula unit of the layer silicate, 0.43 alkylammonium ion and *ca.* 1.58 alkanol molecules are bonded so that a total of two alkyl chains is present.

Since these chains are arranged as a bimolecular film, there are two alkyl chains per formula unit of silicate standing upon each other. Therefore, each step with a shortening of basal spacings by 1.2—1.3 Å corresponds to the formation of one 2g1 kink in one of the two chains only. The enthalpy and entropy changes shown in Table 1 thus refer to formation of one isolated kink in one of the two alkyl chains. The increase in entropy by a constant amount probably indicates that the transition between individual phases is caused by introduction of one further 2g1 kink into the alkyl chains and not (or very rarely) by rearrangement of 2g1 kinks into kinks of higher order as ...tttgt$\bar{g}$ttt... (= 2g1) → ...ttgttt$\bar{g}$tt... (= 2g2) → ...tgttttt$\bar{g}$t... (= 2g3).

A transition enthalpy of 0.7 kcal/mol is evaluated from the experimental data. This is of the same order as the values calculated for kink formation in an isolated *n*-alkyl chain (1.2 kcal/mol) and in a bundle of parallel polyethylene molecules (0.95 kcal/mol)[5]. The fact that the experimental value appears somewhat lower than the other two is probably due to looser packing of the chains in our model system.

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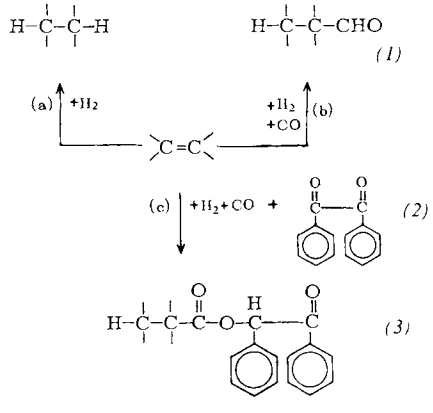
Carboxylic Esters Produced by Low-Pressure Hydroformylation of Olefins in Benzil

By *Kaspar Bott*[*]

Hydrogenation (a) and hydroformylation (b) of olefins catalyzed by transition-metal carbonyl complexes differ in that in the latter reaction the addition of hydrogen is coupled with insertion of carbon monoxide. We now report a new variant (c) of hydroformylation in which hydrogen, carbon monoxide, and benzil react with the olefinic double bond in a definite order.



The α-benzoylbenzyl carboxylates *(3)* formed in this way can be regarded formally as the result of a Tishchenko-Claisen reaction between the aldehyde *(1)* (formed by hydroformylation, *i.e.* an oxo synthesis) and benzil *(2)*. This synthesis requires low pressures of synthesis gas and presence of a rhodium catalyst. The determining intermediate appears to be an acylrhodium compound *(5)* containing a benzil ligand in addition to carbon monoxide; this complex either reacts with hydrogen to give an aldehyde *(1)* or undergoes insertion of *(2)* to yield the ester precursor *(8)*. Finally the rhodium-carbon bond of *(8)* suffers fission by hydrogen.

As the first three examples in Table 1 show, benzil *(2)* can be converted into the ester *(3)* in 80—87% yield

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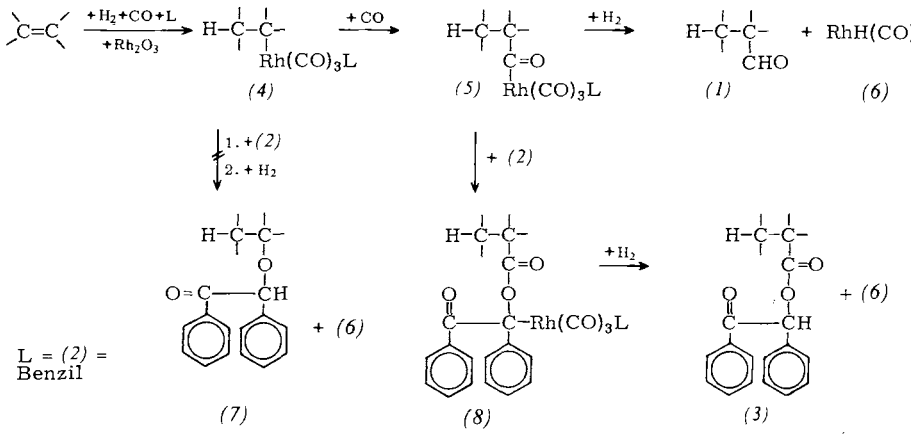

when the reaction is carried out with lower olefins, but the yields decrease considerably with 1-octene and cyclododecene owing to the lower molar olefin conversions.

Table 1. α-Benzoylbenzyl carboxylates *(3)* from benzil *(2)*, olefins, and synthesis gas [a].

Starting olefin	Pressure of synthesis gas [atm] ($H_2/CO = 1:1$)	*(3)*, yield [%] [b]	*(3)*, m.p. [C] or b.p. [C/torr]
1-Butene	25—35	87	150—153/0.1 [d]
Isobutene	35—45 [c]	80	56—57
Cyclohexene	25—30	80	100—101
1-Hexene	30—35	65	163—167/0.1 [d]
1-Octene	30—40	38 [e]	175—180/0.1 [d]
Cyclododecene	50	25 [f]	100—101

[a] General conditions of the synthesis are described in the example.
[b] Olefin and benzil *(2)* were used in equal amounts by weight; the yields refer to benzil.
[c] Total pressure of CO, H_2, and isobutene.
[d] Mixture of isomers shown in Table 2.
[e] Conversion of olefin = 62%.
[f] Conversion of olefin = 76%.

As required by the mechanism proposed, the proportion of benzil incorporated into the ester *(3)* increases with increasing concentration of benzil in the reaction solution and with decreasing partial pressure of carbon monoxide because the rhodium complexes *(4)*—*(6)* and *(8)* exchange the benzil ligand in a reversible reaction for carbon monoxide. If, in the example below, the synthesis gas pressure (molar ratio $CO/H_2 = 1:1$) is increased to 120—140 atmospheres, the yield of α-benzoylbenzyl cyclohexanecarboxylate is then only 16%.

The efficient catalysis of double bond migration by the rhodium-benzil system is surprising; this is shown convincingly by the equality of the isomer ratio of C_5 aldehydes obtained from both 1-butene and 2-butene (Table 2)[1]. Analogously, the hydroformylation of 1-hexene and 1-octene gives rise to formation of branched aldehydes, which must be attributed to the presence of olefins with double bonds in the "interior" of the chain. The oxo synthesis with 1-octene afforded, after 62% conversion, a residual olefin containing less than 4% of "α-isomer".

Table 2 also presents the isomer distribution of the esters *(3)*. It turns out that approximately the same proportions of unbranched aldehydes and unbranched carboxylic esters are formed from 1- and 2-butene and propene. With higher olefins the proportion of unbranched carboxylic acid in *(3)* is very little changed but that of branched aldehyde is increased.

If the phosphane-containing complex $RhH[P(C_6H_5)_3]_2CO$ is used instead of rhodium oxide as catalyst for the low-pressure hydroformylation of propene in benzil, the *n*/iso ratio rises to 69:31 for butyraldehyde and to 68:32 for the butyric ester.

Table 2. Isomer distribution of the hydroformylation products *(1)* and *(3)* from *n*-olefins.

Olefin	Aldehyde *(1)*	Rel. yield [%]	Carboxylic acid in *(3)*	Rel. yield [%]
Propene	2-Methylpropanal	50	2-Methylpropionic	49
	Butanal	50	Butyric	51
1- or 2-Butene	2-Methylbutanal	61—58	2-Methylbutyric	57—58
	Pentanal	39—42	Pentanoic	43—42
1-Hexene	2-Ethylpentanal	17	2-Ethylpentanoic	13
	2-Methylhexanal	48	2-Methylhexanoic	41
	Heptanal	35	Heptanoic	46
1-Octene	2-Propylhexanal	13	2-Propylhexanoic	9
	2-Ethylheptanal	17	2-Ethylheptanoic	12
	2-Methyloctanal	41	2-Methyloctanoic	33
	Nonanal	29	Nonanoic	46

The selectivity for conversion of the olefins into aldehydes *(1)* and esters *(3)* exceeds 90%[4]. Reaction of the alkene with benzil *(2)* and hydrogen, which would lead to the ether *(7)*, could not be detected even in absence of carbon monoxide.

Cyclohexanecarbaldehyde and α-benzoylbenzyl cyclohexanecarboxylate

Cyclohexene (250 g, 3.05 mol), benzil (250 g, 1.19 mol), and Rh_2O_3 (0.10 g) are placed in a 2-l steel autoclave previously purged with nitrogen and are heated at 120 °C with synthesis gas (20 atm cold pressure). The synthesis gas pressure is raised from 25 to 30 atm during the reaction. After 11 hours' reaction, distillation of the autoclave content affords cyclohexanecarbaldehyde (146 g) boiling at 50—56 °C/17 torr and α-benzoylbenzyl cyclohexanecarboxylate (308 g, 80% yield based on benzil), boiling at 175—177 °C/0.2 torr, m.p. 100—101 °C (from light petroleum).

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[1] In contrast to hydroformylation with cobalt catalysts, olefin isomerization due to rhodium catalysis is completely suppressed by complexing agents such as phosphanes [2, 3].

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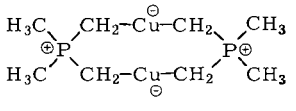
Tetrakis(dimethylphosphoniumbismethylide)-dinickel, a New Type of Cage Compound

By *Hans Heinz Karsch* and *Hubert Schmidbaur*[*]

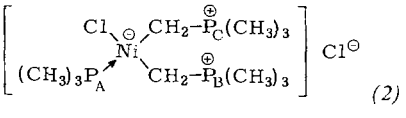
It was shown recently that metal-carbon σ-bonds of ylide complexes are appreciably more stable than those of simple alkyl derivatives. The effect of introducing of an "onium center" on otherwise unstable M—C structural units is exemplified by the unusual properties of the copper compound *(1)* and its homologs[1, 2].



(1)

We now report the synthesis of an analogous nickel compound that has a binuclear structure with no less than four Ni—C σ-bonds attached to each of the two d^8-nickel atoms.

Reaction of dichlorobis(trimethylphosphane)nickel with trimethylmethylenephosphorane[3] in *n*-pentane at room temperature affords a golden-yellow product (dec. 125 °C; yield 93%), whose composition is almost independent of the molar ratio of the reactants and which is insoluble in that solvent or in diethyl ether but soluble in methylene chloride. From the analytical data and particularly from ^{1}H- and ^{31}P-NMR findings it is concluded that it has the salt-like onium structure *(2)*, formed as shown in eq. (1a).



(2)

^{31}P-NMR (CH_2Cl_2, 85% H_3PO_4, H-decoupled, −40 °C)[4]: δP_A +19.9 ppm, d, $J(P_ANiCP_B)$ 15.2 Hz; δP_B −23.6, dd, $J(P_BCNiP_C)$ 3.4; δP_C −24.5, d, $J(P_ANiCP_C)$ 0.

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^{1}H-NMR (ext. TMS, other conditions as above)[4]: τCH_3P_A 8.82 ppm, d, $J(HCP_A)$ 8.1 Hz; τCH_3P_B 8.10, d, $J(HCP_B)$ 13.4; τCH_3P_C 8.02, d, $J(HCP_C)$ 13.5; τCH_2P_B 9.60, dd (broad), $J(HCP_B)$ 16.1, $J(HCP_A) \approx 13$; τCH_2P_C 9.48, dd (broad), $J(HCP_C)$ 16.2, $J(HCP_A) \approx 6$.

However, when the above-mentioned reactants are mixed, not in *n*-pentane, but in tetrahydrofuran at 0 °C, or when the product *(2)* is treated in that solvent with an excess of the ylide, a colorless precipitate of tetramethylphosphonium chloride is formed together with a yellow product *(3)* that is soluble in ether, benzene or toluene and is volatile in a vacuum (sublimes at 45 °C/0.1 torr, dec. 87 °C; yield 23%); at the same time a second molecule of trimethylphosphane is liberated [eq. (1b)].

$$2\,(CH_3)_3P + 4\,(CH_3)_3P{=}CH_2 + 2\,(2) \qquad (1a)$$

$$2\,[(CH_3)_3P]_2NiCl_2 + 8\,(CH_3)_3P{=}CH_2 \xrightarrow[\text{THF}]{\text{n-pentane}}$$

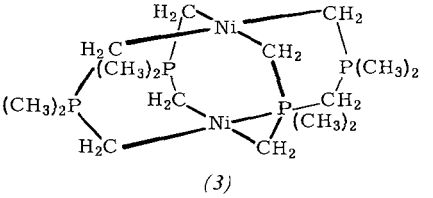
$$4\,(CH_3)_3P + 4\,[(CH_3)_4P]Cl + [(CH_3)_2P(CH_2)_2]_4Ni_2 \qquad (1b)$$

(3)

The complex *(3)* formed by two-fold metalation of the ylide is shown by cryoscopic determination of its molecular weight to be a dimer[5]. The molecular ion of the dimer appeared in the mass spectrum only at low ionization energies and high target temperature (18 eV, 85 °C), but then had the expected isotope distribution. Spectra measured at 70 eV and 30 °C, however, show only the ions of the monomer *(4)*[6].

The ^{1}H-NMR spectra of toluene solutions show only two 1:1 doublets with a 3:2 ratio of areas in the temperature range +80 to −80 °C: τCH_3P 8.77 ppm, $J(H_3CP)$ −11.9 Hz; τCH_2P 11.9, $J(H_2CP)$ −4.8. P-Decoupling leads to singlets. Double-resonance experiments prove that $J(H_2CP)$ and $J(H_3CP)$ have the same sign. In the H-decoupled ^{31}P-NMR spectrum δP, at 1.7 ppm, appears in the region for tetracoordinated onium centers[7]. The IR and Raman absorptions correspond largely to those of *(1)* and its homologs: strong bands at 665, 638 and 467 cm^{-1} can be assigned to vibrations of the skeleton of heavy atoms.

Taking our results as a whole we propose for *(3)* a structure in which two parallel square-planar $Ni(CH_2)_4$ units[8] are bonded together by four dimethylphosphonium groups.



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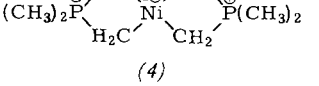

(4)

Models indicate that such a type of bonding can be strain-free. In this structure the eight-membered ring unit of *(1)* is present twice, as in the string by which a parcel is tied up. It is conceivable that the monomer *(4)* is in equilibrium with *(3)* under the conditions of the mass

spectroscopy. We are describing other ylide complexes of nickel elsewhere[9].

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[3] *H. Schmidbaur* and *W. Tronich*, Chem. Ber. *101*, 595 (1968).

[4] The assignment of P_B and P_C rests on analogy with findings for other square-planar alkylnickel compounds [9]. The decision is not conclusive.

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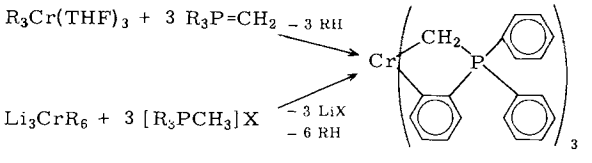
Synthesis of Tris(dimethylphosphoniumbismethylide)chromium(III)

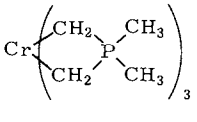
By *Erhard Kurras, Uwe Rosenthal, Herbert Mennenga*, and *Günther Oehme*[*]

Schmidbaur et al. recently described organic ylide complexes of copper, silver[1] and gold[2]. We have found[3] that reaction of methylenetriphenylphosphorane with triphenyltris(tetrahydrofuran)chromium[4] or of a methyltriphenylphosphonium halide with lithium hexaphenylchromate(III)[5] leads to the chelate complex *(1)* by *ortho*-metalation of a phenyl group of the ylide.



R = C_6H_5; X = Cl, Br, I *(1)*

However, interaction of lithium hexaphenylchromate(III) and tetramethylphosphonium chloride in tetrahydrofuran under anaerobic conditions affords analogously tris(dimethylphosphonium bismethylylide)chromium(III) *(2)*.



(2)

The latter product can also be prepared by treating $CrCl_3(THF)_3$[6] with methylenetrimethylphosphorane that has been metalated by methyl- or phenyl-lithium[7]:

$$[(CH_3)_4P]Cl + 2LiCH_3 \xrightarrow{\text{Ether}} [(CH_3)_2P(CH_2)_2]Li + 2CH_4 + LiCl$$

$$3[(CH_3)_2P(CH_2)_2]Li + CrCl_3(THF)_3 \xrightarrow{THF} (2) + 3LiCl$$

Compound *(2)* crystallizes in red needles that are extremely sensitive to oxidation and hydrolysis, melt in the region 59—68 °C, dissolve very readily in solvents that do not contain active protons (*e.g. n*-hexane, benzene, toluene or ether), and can be sublimed in a vacuum (10^{-3} torr, 30 °C). The compound is paramagnetic ($\chi_g = 16.42 \cdot 10^{-6}$ $cm^3\ g^{-1}$, 293 °K)[8]. The effective magnetic moment μ_{eff} is 3.6 μ_B, corresponding to Cr^{III} with the d^3 configuration.

The characteristic fragments, $m/e = (M-L)$ 230 (35.6%), $(M-2L)$ 141 (100) and Cr 52 (34.2) can be seen alongside the molecular ion, 319 (38.3) in the mass spectrum (70 eV; input temperature 20, ion source 270 C; LKB 9000).

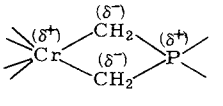
In the IR spectrum (Beckman IR 12; 0.1 M in *n*-hexane; $d = 0.1$ mm) the following bands (in cm^{-1}) are found in the regions free from solvent absorptions: 390(w), 431.5(s), 551.5(m), 660(m), 737(m), 760.5(s), 813.5(m), 933.5(vs), 970(m,sh), 1278.5(m), 1288(m), 1339(m), 1410(w), 1418(w,sh), 1425(w). The bands at 970 and 933.5 cm^{-1} are to be ascribed to the antisymmetrical and symmetrical P—C stretching vibrations; as expected, the frequencies are shifted to longer wavelengths compared with those of the free ylide ($\nu_{P=C}$: 1006 cm^{-1}[9]). In the lower frequency region the bands at 431.5 and 390 or, more probably, those at 552.5 and 431.5 cm^{-1} correspond to the antisymmetrical and symmetrical Cr—C stretching vibrations.

Compound *(2)* gives typical reactions of organometallic compounds. In ethereal solution it reacts with, for instance, carbon dioxide and benzophenone. The phosphonium salt formed by protolysis according to the equation

$$(2) + 6HCl \xrightarrow{THF} CrCl_3(THF)_3 + 3[(CH_3)_4P]Cl$$

was isolated and characterized as chloride and tetraphenylborate.

These findings indicate an octahedral arrangement of the C—Cr—C units. It is less likely that there is electron delocalization in the $>C{=}PMe_2{-}\overset{(-)}{C}<$ group as in the allyl group[10], by analogy with tris(allyl)chromium[11], together with involvement of the phosphorus. The charge distribution shown schematically in *(3)* clearly stabilizes the polar Cr—C σ-bond, and Cr—P interaction is not be excluded.



(3)

An X-ray structure analysis of *(2)* is in progress.

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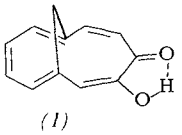
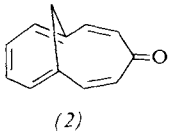
Crystal Structure of 2-Hydroxy-4,9-methano[11]annulenone

By *D. W. J. Cruickshank*, *G. Filippini*, and *O. S. Mills*[*]

Recently the synthesis of a number of 10 π-electron analogs of tropone[1] and of tropolone[2], and structure analyses of two [11]annulenones[3,4] have been reported. In this communication we present the essential structural results for 2-hydroxy-4,9-methano[11]annulenone *(1)*[2][**]. Compound *(1)* crystallizes in the triclinic system, space group $P\bar{1}$ with $a=8.448$, $b=8.184$, $c=7.803$ Å; $\alpha=110.10$, $\beta=69.09$, $\gamma=92.38$. The analysis is based upon 1639 reflections measured on a computer-controlled diffractometer, the structure was solved by direct methods and refined by least-squares techniques; the final R is 6.0%.



(1)



(2)

In preparation for the discussion of *(1)* it should be noted that definitive structural evidence now exists to show that tropone itself exists as a near-planar (slightly-boat conformation) molecule with alternating single and double bonds[5], that its derivatives[6] display similar features, and that tropolone and substituted tropolones seem also to manifest alternation of bond length[7].

We find (see Figure 1) that in *(1)* there is evidence both of an alternation of bond lengths and of delocalization within the same molecule; the eight-membered ring, which contains the α-hydroxyketone group, has two formal double bonds whose (independent) lengths are 1.353 Å, little more than the standard value for an isolated double bond[8]. The C—C bond lengths in the cycloheptatriene ring, excluding those to the methylene bridge, however show only a small variation in lengths between 1.376 and 1.399 Å.

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[**] We are grateful to Prof. *E. Vogel* for supplying us with crystals of *(1)*.

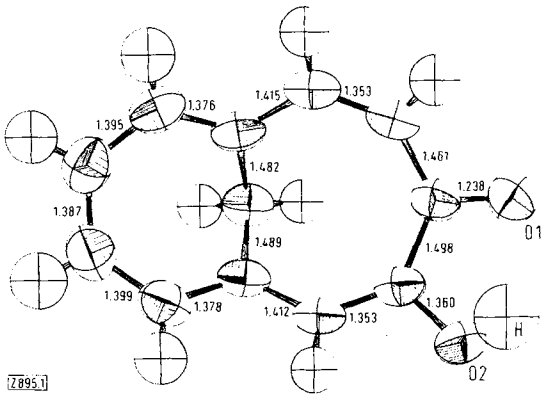

Fig. 1. Crystal structure of 2-hydroxy-4,9-methano[11]annulenone *(1)*.

We therefore suggest that considerable delocalization occurs in that ring, more than in either 4,9-methano[11]annulenone *(2)* (1.366—1.422 Å) or in 1,6-methano[10]annulene-2-carboxylic acid (1.378—1.426)[9], and more still than in cycloheptatriene (1.356—1.446 Å)[10] or its derivatives (*e.g.* 1.35—1.45 Å)[11].

The ^{1}H-NMR values reported for *(1)*[2] are in agreement with our findings. The multiplet which extends over the region $\tau=2.5$—3.2 is positioned similarly to that reported for 1,6-methano[10]annulene[12] in which a delocalized system is recognized (for bond lengths see ref. [9]), whereas in cycloheptatriene values of $\tau=3.4$—3.9 occur. Such delocalization might be expected to be associated with a pronounced ring current and consequential difference in absorption of the *syn* and the *anti* protons of the methylene group. The observed difference, 0.7 τ-units, must be the resultant of the deshielding effects of the ring current on the one proton and of the C=O group on the other. When comparison is made of the spectrum of *(1)* with that of *(2)*, however, it is important to note the change of shape between the two molecules; *(1)* is more planar than *(2)*, possibly because the hydrogen bond is *intra*-molecular, in contrast to the case of crystalline tropolone[7]. The effect of this change of shape is to increase the transannular distance between the *anti*-methylene hydrogen and the carbonyl carbon from 2.46 Å in *(2)* to 2.64 Å in *(1)*.

In the present analysis we have determined, and satisfactorily refined, the positions of all the hydrogen atoms and we confirm from these direct observations, as well as infer from the positions of the double bonds, that the hydroxyl group is located on C-2[2].

The overall structure has close to mirror symmetry perturbed only by the hydroxyl group. The C—O distances in the carbonyl and hydroxyl groups are in good agreement with usually accepted values.

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Triiodogermane[**]

By *Friedrich Höfler* and *Ernst Brandstätter*[*]

Of the various trihalogermanes, only $HGeCl_3$ and $HGeBr_3$ have been previously reported; they tend to decompose according to eq. (1b)[1] or to GeX_4, GeX_2 and H_2[2]. Triiodogermane, $HGeI_3$, has been merely conjectured as an intermediate in germylation reactions of olefins with GeI_2/50% aqueous HI[3,4].

Since we succeeded in preparing pure, $GeBr_4$-free $HGeBr_3$ by dissolving $GeBr_2$[5] in anhydrous HBr, we have found also that $HGeI_3$ is formed in quantitative yield when anhydrous HI is condensed on pure GeI_2 [eq. (1a)]:

$$GeX_2 + HX \underset{b}{\overset{a}{\rightleftharpoons}} HGeX_3 \qquad (1)$$

The pale yellowish solution is stable below $-50\,^{\circ}C$ but at room temperature decomposes gradually thus:

$$HGeI_3 + HI \rightarrow GeI_4 + H_2 \qquad (2)$$

(*ca.* 50% after 7 days); dismutation to H_2GeI_2 and GeI_4 was not observable. When the solvent HI is removed, even at low temperature, only GeI_2 is left as solid residue [eq. (1b)]; and other attempts to prepare it—by $HGeCl_3$/HI, $HGeCl_3$/GeI_4 or $HGeCl_3$/$HSiI_3$ as reactants—lead also to GeI_2. However, $HGeI_3$ is formed smoothly when an excess of HI is condensed on $GeBr_2$, but in a suspension of GeI_2 in 57% aqueous HI we could not prove the formation of triiodogermane.

Thus $HGeI_3$ can exist only in liquid HI. But in such solutions we could measure the Raman spectrum, and this showed, as required for a C_{3v} molecule, three polarized and three depolarized lines (Table 1). The frequencies are in the expected regions, which can be derived from correlations and calculations for comparable vibrations for the series $HGeX_3$ (X = Cl, Br[6] or I) and $HGeX_3$/GeX_4.

Table 1. Fundamental vibrations (cm^{-1}) from the Raman spectrum of $HGeI_3$.

Type		$\tilde{\nu}$	Assignment
A_1	ν_1	2068 (0.5, p)	νGeH
	ν_2	203 (10, p)	$\nu_s GeI_3$
	ν_3	93 (5, p)	$\delta_s GeI_3$
E	ν_4	260 (1.5, dp)	$\nu_{as} GeI_3$
	ν_5	66 (6, dp)	$\delta_{as} GeI_3$
	ν_6	643 (0.6, dp)	δHGeI

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νGeH and δHGeI are slightly dependent on concentration, being 5—8 cm^{-1} higher for very dilute solutions.

In the reaction of stoichiometric amounts of HI with $GeBr_2$ or a $GeBr_4$/GeI_2 mixture there are formed, besides $HGeI_3$, the trihalides $HGeBrI_2$ and $HGeBr_2I$, which also cannot be isolated but can be recognized from their main frequencies in the Raman spectrum (220 vs,p and 239 cm^{-1} vs,p).

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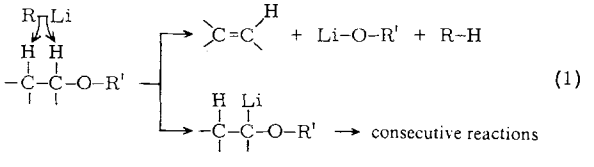
Nucleophilic Ether Fissions by 1,1-Diphenylhexyllithium[**]

By *Gert Köbrich* and *Annegrit Baumann*[*]

Because of the role of ethereal solvents in reactions of organometallic compounds, fission of ethers by organometallic and in particular organolithium compounds is very important. According to earlier investigations it is normally initiated by deprotonation at the α- or β-carbon atom of the ether[1]; very recent investigations[2] have uncovered an interesting meshing of α-,β- and,α',β-eliminations for the case of diethyl ether/alkyllithium. We propose to collect together under the general expression "protophilic ether fission" all those fissions that have proton abstraction from the ether molecule in the first reaction step as their common characteristic [eq. (1)]:

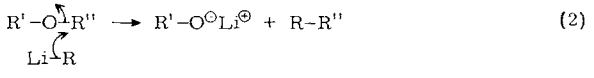
Protophilic ether fission:



(1)

We now report "nucleophilic ether fission" as a further type of reaction. This is a nucleophilic replacement by the organolithium compound [eq. (2)], in which an RO group of the ether constitutes the leaving group, thus playing the same role as do halogen atoms in the coupling of alkyl halides.

Nucleophilic ether fission:



(2)

If we let aside those reactions, formally similar but different in kind, in which complex formation at the oxygen atom by a Lewis acid is the first step, as with triphenylmethyl an-

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ions in presence of triphenyl-borane or -aluminum[3a] and very probably with Grignard reagents[3b], then nucleophilic ether fission has been observed only with oxiranes[4a] and oxetanes[4b], which contain strained rings, and moreover only occasionally with tetrahydrofuran (THF) (with R_3SiLi[5a] or triphenylmethyllithium[5b]).

As organometallic reagent we used 1,1-diphenylhexyllithium (DPHLi)[6], which smoothly splits not only cyclic ethers but also alkyl phenyl, allyl and vinyl ethers (Table 1). In all these cases nucleophilic predominates over protophilic fission, as is made evident by the poor yields of 1,1-diphenylhexane (DPH—H) which is the protonation product of DPHLi. Product analyses permit the following generalizations:

1. With cyclic ethers the ease of reaction increases with decreasing ring size, corresponding to increasing ring strain. Tetrahydropyran is no longer attacked nucleophilically; and its protophilic fission by DPHLi at 70°C also occurs only to a small extent, so that this compound is more suitable as solvent for reactions involving DPHLi than is the commoner but less resistant THF.

2. Whereas the alkyl group of alkyl phenyl ethers is transferred to DPHLi [eq. (3)], it is the unsaturated group of alkyl vinyl ethers that is given up [eq. (4)]. This "transpoling" indicates an addition-elimination reaction as mechanism for the vinyl ether fissions; it is faster than the S_N2-like transfer of alkyl groups.

$$DPHLi + C_6H_5{-}O{-}Alkyl \rightarrow DPH\text{-}Alkyl + C_6H_5{-}OLi \quad (3)$$

$$DPHLi + CH_2{=}CH{-}O\text{-}Alkyl \rightarrow DPH{-}CH{=}CH_2 + Alkyl\text{-}OLi \quad (4)$$

3. Allylic rearrangement can accompany fission of substituted allyl ethers: 3-phenoxy-1-butene affords only the thermodynamically favored, rearranged product with the 2-butenyl structure. The preponderating product from the isomeric 4-phenoxy-2-butene in THF is the unrearranged product, but in hexane (in presence of 1 mol of tetramethylethylenediamine) it is mainly the unrearranged, sterically disfavored coupling product (Table 1). Product formation is thus influenced by the reaction medium.

4. Allyl ether bonds are particularly easily split; even anionized allyl alcohol is smoothly cleaved (1:1, 6h at 70 C in THP, relative yield 100%) [eq. (5)]:

$$DPHLi + CH_2{=}CH{-}CH_2{-}\overset{\ominus}{O}\overset{\oplus}{Li} \rightarrow DPH{-}CH_2{-}CH{=}CH_2 + Li_2O \quad (5)$$

5. The relative rates of nucleophilic fission of C—O bonds by DPHLi decrease in the order Allyl—O— > Vinyl—O— > Alkyl—O— ≫ Phenyl—O—.

Many of the ethers included in Table 1 were treated with benzhydryllithium instead of DPHLi, and the results were qualitatively identical and quantitatively similar. It is probable that nucleophilic ether fission is a characteristic reaction of mesomeric carbanionoids, being caused by the fact that their basicity is lower than that of other organolithium compounds and that their nucleophilicity is high, the latter being made evident by their extremely rapid coupling with alkyl halides[8].

Table 1. Conditions and products of the reaction of 1,1-diphenylhexyllithium (DPHLi) with ethers [6, 7].

Ether	Ether: DPHLi	Reaction conditions [b]	Products and relative yields [d]
a) Cyclic ethers			
Oxirane	1:1	At 0 C instantaneous in THF	DPH—CH_2—CH_2—OH (70%) + DPH—H (30%)
Oxetane	1:1	12h at room temp. in THP	DPH—CH_2—CH_2—CH_2—OH (100%)
Tetrahydrofuran (THF)	[a]	120h at room temp. and 22h at 70°C	DPH—CH_2—CH_2—CH_2—CH_2—OH (84%) + DPH—H (16%)
Tetrahydropyran (THP)	[a]	96h at room temp. and 22h at 70°C [conversion 16%]	DPH—H (16%)
b) Acyclic ethers			
$H_2C{=}CH{-}O{-}C_4H_9$-*n*	2:1	72h at room temp. and 10h at 70 C in THP	DPH—$CH{=}CH_2$ (95%) + DPH—H (5%)
$H_2C{=}CH{-}O{-}C_4H_9$-iso	2:1	72h at room temp. and 10h at 70 C in THP	DPH—$CH{=}CH_2$ (92%) + DPH—H (8%)
$C_6H_5{-}O{-}CH_3$	[a]	18h at room temp.	DPH—CH_3 (90%) + DPH—H (<10%)
$C_6H_5{-}CH{=}CH{-}O{-}CH_3$	1:1	22h at room temp. in $(C_2H_5)_2O$	DPH—CH=CH—C_6H_5 (*trans* 78%, *cis* 14%) + DPH—CH_3 (5%) + DPH—H (3%)
$C_6H_5{-}O{-}CH_2{-}CH{=}CH{-}CH_3$	1:1	15h at room temp. in THF	DPH—CH_2—CH=CH—CH_3 (94%) + DPH—$CH(CH_3)$—$CH{=}CH_2$ (6%)
	1:1	48h at room temp. in hexane [c]	DPH—CH_2—CH=CH—CH_3 (9%) + DPH—$CH(CH_3)$—$CH{=}CH_2$ (91%)
$C_6H_5{-}O{-}CH(CH_3){-}CH{=}CH_2$	1:1	3h at room temp. in THF	DPH—CH_2—CH=CH—CH_3 (100%)
	1:1	36h at room temp. in hexane [c]	DPH—CH_2—CH=CH—CH_3 (100%)

[a] The ether studied served as solvent.
[b] The DPHLi was completely consumed, unless stated otherwise.
[c] In presence of 1 equivalent of tetramethylethylenediamine.
[d] Referred to DPHLi; about 80—90% thereof was isolated.

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[6] 0.5 M DPHLi solutions used were free from lithium salts; they were prepared from 1,1-diphenylethylene and *n*-butyllithium in light petroleum. The reactions were terminated by addition of an excess of *n*-butyl bromide [8b].

[7] The products were separated by column chromatography. Their structures were proved by elemental analyses and by spectroscopy, and in some cases by comparison with samples prepared by independent methods. The relative yields shown in Table 1 were determined by gas chromatography with the aid of pure samples.

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Spiro[3.4]octa-5,7-diene[**]

By *Armin de Meijere* and *Lüder-Ulrich Meyer*[*]

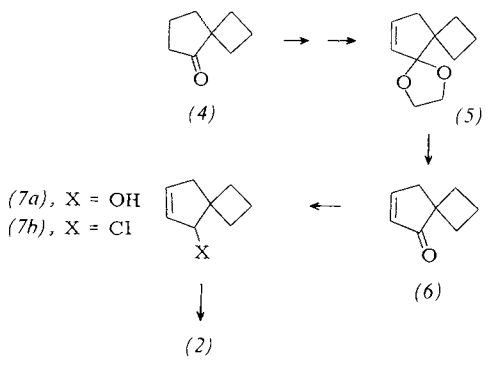
Dedicated to Professor H. Brockmann on his 70th birthday

Whereas the spiro[*n*.4]alkadienes *(1)* and *(2)* are readily accessible by cycloalkylation of the cyclopentadienyl anion by, respectively, 1,2-dibromoethane and 1,4-dibromobutane[1], the analogous reaction with 1,3-dibromopropane does not lead to *(2)*[2]. We report here the preparation and some of the chemical and spectroscopic properties of the hydrocarbon *(2)*.

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

Compound *(2)* is of interest in comparison with *(1)* and *(3)* which differ greatly in their behavior in the Diels-Alder reaction[6] and on gas-phase pyrolysis[5, 7], and also because of a possible electronic interaction between the π-orbitals of the diene component and the C—C bonding orbitals of the cyclobutane ring[8].

Our starting material was spiro[3.4]octan-5-one *(4)*[9]. On successive bromination in ethylene glycol, dehydrobromination by potassium hydroxide in methanol and hydrolysis of the acetal *(5)* this afforded the ketone *(6)*[11] (yield through 3 steps: 54%), this sequence being analogous to *Garbisch*'s general procedure[10]. Attempts to prepare the tosylhydrazone of *(6)*, and thence *(2)* by treatment with methyllithium[12], failed: 1,4-addition of tosylhydrazide to *(6)* was observed in all these attempts. However, reduction of *(6)* by aluminum hydride[13] yielded the alcohol *(7a)* (74%); subsequent treatment with thionyl chloride in tetrahydrofuran/pyridine at room temperature led to 5-chlorospiro[3.4]oct-6-ene *(7b)* (53%). Dehydrochlorination of *(7b)* by potassium *tert*-butoxide in tetraethyleneglycol dimethyl ether (tetraglyme) at room temperature in a vacuum (0.01 = torr)[14] afforded the diene *(2)* (yield 67%, determined by gas chromatography); this



compound distilled in the process, together with some *tert*-butyl alcohol, into a trap cooled in liquid nitrogen and was obtained pure by preparative gas chromatography[11].

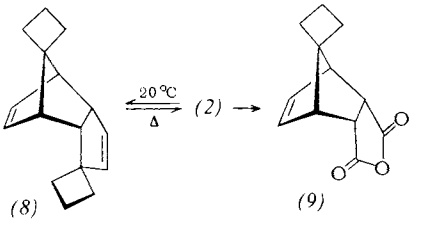
In its ^{1}H-NMR spectrum (CCl_4), *(2)* shows multiplets at $\tau = 3.61$ and $\tau = 3.91$ (each 2H, AA'BB' system of the olefinic protons) and at $\tau = 7.79$ (6H, cyclobutyl protons). The IR spectrum of *(2)* is not characteristic and does not accord with that reported by *Chiurdoglu* and *Tursch*[3]. The longest-wavelength absorption lies at 257 nm, as does that of *(1)* (see Table 1).

Table 1. UV data of the spiro[*n*.4]alkadienes *(1)*—*(3)* and of 5,5-dimethyl-1,3-cyclopentadiene [in ethanol, *(2)* in *n*-pentane].

Cpd.	λ_{max} [nm]	ε_{max}	λ_{max} [nm]	ε_{max}	Ref.
(1)	223	6300	257	2700	[15]
(2)	<200	—	257	1500 [a]	
(3)	<210	—	254	2750	[15]
(13)	<210	—	250	2900	[15]

[a] The extinction coefficient found may be too small because *(2)* dimerizes very rapidly at room temperature.

In its chemical behavior, *(2)* resembles *(3)* rather than *(1)*. Pure *(2)* dimerizes rapidly at room temperature to give *(8)*[11]. ^{1}H-NMR (CCl_4) of *(8)*: $\tau = 4.37$ (m, 2H); 4.50 (m, 1H); 4.83 (m, 1H); 6.78 (m, 1H); 7.51 (m, 3H); 8.35 (m, 12H). The half-reaction time for dimerization in dilute solution (0.86 M in CCl_4) at 50 C amounts to *ca.* 2.3 h.



On treatment with maleic anhydride in benzene (50 C, 5 h), *(2)* affords the Diels-Alder adduct *(9)*[11] (70%; m. p. 86 C; colorless crystals), ^{1}H-NMR ($CDCl_3$): $\tau = 3.81$ (t, 2H); 6.47 (dd, 2H); 6.79 (m, 2H); 8.22 (m, 6H).

Thermal rearrangement of *(2)*, which ring strain should cause to be much easier than that of *(1)* and *(3)*[16], has so far been examined only qualitatively. In a flow pyrolysis apparatus at 400 °C a 1:0.8 mixture of the isomeric bicyclo[3.3.0]octadienes *(11)* and *(12)* was formed. Thermal decomposition of the dimer *(8)* led under these conditions to a product mixture of the same composition. *(11)* and *(12)* can be separated by gas chromatography and identified by means of their ^{1}H-NMR spectra[17].

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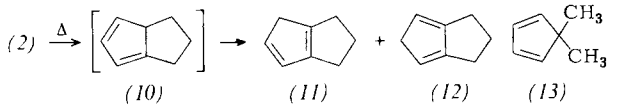

(10) (11) (12) (13)

It is probable that (2) yields, by a [1.5]-alkyl shift, first the compound (10), which then undergoes [1,5]-hydride shifts, yielding (11) and (12), under the conditions used.

The problem of the interaction between the cyclobutane ring and the diene portion of (2) is to be investigated by photoelectron spectroscopy (PES)[18]. Qualitative consideration of the PE spectrum of (2) and its comparison with that of (1)[19] indicate that such an interaction does occur[18].

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[17] (11), ^{1}H-NMR (CCl_4): $\tau = 3.83$ (m, 2H); 7.39 (m, 2H); 7.72 (m, 6H). (12), ^{1}H-NMR (CCl_4): $\tau = 4.37$ (m, 2H); 6.91 (m, 2H); 7.75 (m, 6H). Cf. O. Süs and K. Möller, Liebigs Ann. Chem. 593, 91 (1956).

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A New Approach to the Synthesis of Oligodeoxyribonucleotides[**]

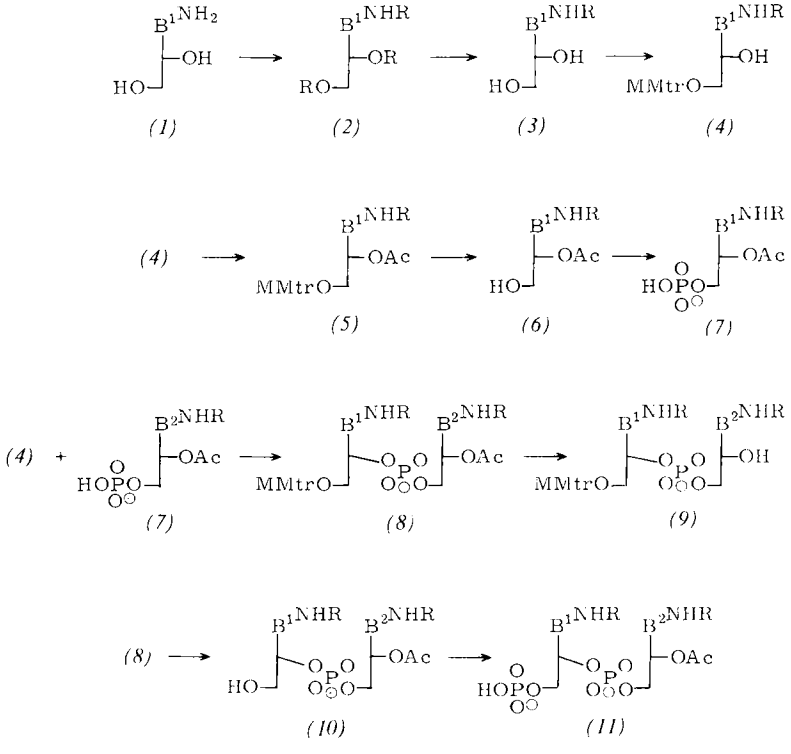
By Hubert Köster and Walter Heidmann[*]

Dedicated to Professor Friedrich Cramer on the occasion of his 50th birthday

For the synthesis of double-stranded polydeoxynucleotides with defined sequences by the standard methods[1], short chemically synthesized oligodeoxyribonucleotides are phosphorylated at the free 5'-OH group using the enzyme polynucleotide kinase and ATP and then joined with the enzyme polynucleotide ligase. The synthesis of these short oligodeoxyribonucleotides starts favorably with a 5'-blocked deoxynucleoside. For the elongation, 3'-*O*-protected deoxyribonucleoside 5'-phosphates (or 3'-*O*-protected deoxyribonucleoside diphosphates or trideoxyribonucleoside triphosphates) are necessary. To achieve unequivocal 3'-5'-internucleotidic linkage, the amino groups of the heterocyclic bases also have to be protected. Therefore a large number of intermediates [compounds of type (4), (7), and (11)] have to be prepared during synthesis of a long double-stranded polydeoxyribonucleotide.

We have developed a new approach which decreases the expense of such syntheses by using only a few key intermediates for many different reaction pathways.

We have been able to phosphorylate 3'-*O*-acetylated deoxyribonucleosides (6) almost quantitatively with phosphorus oxychloride to give the 3'-*O*-acetylated deoxyribonucleoside 5'-phosphates (7). Compounds of type (6) could easily be obtained by acetylation and subsequent detritylation of the 5'-monomethoxytritylated deoxyribonucleosides (4) which have to be prepared for the chain starts. The first extension of (4) by reaction with (7) leads to 5'-monomethoxytritylated deoxyribonucleoside monophosphates (8), which are obtainable in pure form with high yields in a short time by extraction procedures. After



Scheme 1. Synthesis of oligodeoxyribonucleotides. R = benzoyl, anisoyl, isobutyl; Ac = acetyl; MMtr = monomethoxytrityl; B = adenine, guanine, cytosine, thymine (without NH_2).

de-*O*-acetylation to give (9), this compound is ready for the next chain elongation step. Removal of the monomethoxytrityl group from compound (8), however, leads after direct phosphorylation with phosphorus oxychloride to the 3'-*O*-acetylated dideoxyribonucleoside diphosphates (11), which can be used as blocks for the chain elongation (Scheme 1).

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It is important to use a sterically hindered base such as 2,6-lutidine by which the reactivity of the other chlorine atoms is very much reduced. Tetrahydrofuran is used as a solvent for the phosphorylation of the 3'-*O*-acetylated deoxyribonucleosides *(6)*. The phosphorylation of *(10)* takes place in a heterogeneous medium. Of particular importance here is the choice of the liquid phase, which leads to a stable suspension. This is summarized in Figure 1, together with some yields.

Table 1. Phosphorylation of dX(Ac) and dX—dY(Ac) with $PZCl_3$ (Z = O, S).

Cpd. [2]	Z	Phosphorylation [%]	Solution or suspension medium
dT(Ac)	O	95	tetrahydrofuran
dT(Ac)	S	75	tetrahydrofuran
dbz^6A(Ac)	O	97	tetrahydrofuran
dT—dT(Ac)	O	54	tetrahydrofuran
dT—dan^4C(Ac)	O	72	diethyl ether with 20% tetrahydrofuran
dbz^6A—dT(Ac)	O	51	diethyl ether with 20% tetrahydrofuran
dan^4C—$dibu^2G$(iBu) [3]	O	57	diethyl ether with 10% petroleum ether
$dibu^2G$—$dibu^2G$(iBu) [4]	O	63	diethyl ether with 40% petroleum ether

The method described here has the following advantages:

1) Oligodeoxyribonucleotides can be synthesized starting with the relatively inexpensive deoxyribonucleosides.

2) The four 5'-protected deoxyribonucleosides are starting materials both for the synthesis of the chain starts, and for the synthesis of the 3'-*O*-acetylated deoxyribonucleoside 5'-phosphates, which are necessary for the elongation of the chain.

3) The protected dideoxyribonucleoside monophosphates—obtained during chain synthesis—can be used as starting material for the synthesis of 3'-*O*-acetylated dideoxyribonucleoside diphosphates, which are necessary for the extension of the chain.

4) Compounds of type *(4)*, *(7)*, *(8)*, and *(11)* can be obtained pure in large amounts in a short time.

Extension of this approach to the synthesis of trinucleoside triphosphates is now under investigation.

3'-O-Acetyldeoxyribonucleoside 5'-phosphates (7):

(6) (1 mmol) is evaporated three times with dry 2,6-lutidine, dissolved in tetrahydrofuran (8 ml), 2,6-lutidine (1.75 ml, 15 mmoles) is then added. The mixture is cooled in an ice bath and freshly distilled phosphorus oxychloride (0.138 ml, 1.5 mmol) is added with stirring. After 15 minutes the cooling bath is removed. After a further 15 minutes, the reaction mixture is hydrolyzed with 0.2 M aqueous triethylammonium acetate (12 ml) (pH 7) and after standing for 12 hours the reaction mixture is evaporated several times with water. The inorganic phosphate is precipitated at pH 7 with barium acetate according to known procedures. The solution is then adsorbed onto a column of DEAE-cellulose (acetate form), traces of unreacted *(6)* are removed by washing with 25 mM aqueous triethylammonium acetate containing 40% methanol. Then *(7)* is eluted with 150 mM aqueous methanolic triethylammonium acetate, evaporated, dried several times by evaporation with pyridine and then precipitated into ether.

3'-O-Acetylated dideoxyribonucleoside diphosphates (11):

(10) (1 mmol, as 2,6-lutidinium salt) is made into a fine suspension by vigorous shaking with some glass beads (diameter 2—3 mm) in the presence of the appropriate mixture (4 ml) (Fig. 1) and of 2,6-lutidine (2.91 ml, 25 mmol). The suspension is cooled to −10 C, freshly distilled phosphorus oxychloride (0.23 ml, 2.5 mmol) is added, and the mixture shaken vigorously for 15 minutes. After 1 hour it is hydrolyzed with 0.3 M aqueous triethylammonium acetate (4 ml) (pH 7) for at least 12 hours at 0 °C. Then follows chromatography on DEAE-cellulose (acetate form). Lutidine and unreacted *(10)* are washed out with 25 mM triethylammonium acetate containing 40% methanol. *(11)* is eluted using a gradient of triethylammonium acetate (linear from 25 mM to 250 mM and from 250 mM to 400 mM) containing 40% methanol. The fractions, which contain *(11)*, are collected, evaporated, dried by evaporation with pyridine, and precipitated into ether.

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German version: Angew. Chem. 85, 871 (1973)

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[3] Prepared by Dipl.-Chem. *H. Blöcker*.

[4] Prepared by Dipl.-Chem. *S. Geussenhainer*.

The Versatile (Polypyrazolyl)borates

By *Swiatoslaw Trofimenko*[*]

(Polypyrazolyl)borates of the general formula $[R_nB(pz)_{4-n}]^-$ ($n=0$, 1 or 2; R=H, F, Alkyl or Aryl; pz=1-pyrazolyl which may be C-substituted) are a new class of anion that has a well-developed tendency to form chelate compounds and can function as a bi-, tri- or even a quadridentate ligand[1, 2].

The bidentate ligands $R_2B(pz)_2^-$ and bivalent transition-metal ions form neutral chelate compounds $[R_2B(pz)_2]_2M$ that resemble those from 1,3-diketones but are always monomeric. With carbonylmetal compounds, *e.g.* $Mo(CO)_6$, they form anionic tetracarbonyl complexes that are readily converted by reaction with allyl halides into formally 16-electron complexes such as $(C_2H_5)_2B(pz)_2Mo(CO)_2$-π-$C_3H_5$ or $H_2B(pz')_2Mo(CO)_2$-π-C_3H_5. The last of these compounds contains a B—H—Mo bridge, which accounts for its chemical stability[3].

The tridentate ligands $RB(pz)_3^-$ afford not only chelates $[RB(pz)_3]_2M$ of D_{3d} symmetry that resemble metallocenes and are very stable thermally and chemically, but also compounds such as $RB(pz)_3Mo(CO)_2N{=}NAr$ that are analogous to half-sandwich compounds. Although these compounds resemble the analogous C_5H_5 complexes, most of them are considerably more stable both chemically and thermally; for example, $HB(pz)_3^-$ forms a stable monocarbonylcopper derivative $HB(pz)_3Cu(CO)$[4].

The ligand $B(pz)_4^-$ can appear doubly bidentate and afford spiro cations such as $[\pi\text{-}C_3H_5Pd(pz)_2B(pz)_2Pd\text{-}\pi\text{-}C_3H_5]^+$[5]. Various types of stereochemical instability have been studied by NMR spectroscopy with the aid of (polypyrazolyl)borates.

Although the (polypyrazolyl)borates form only σ- and not π-bonds to metals, their chelate compounds are very stable; in many cases such borates displace phosphane and cyclopentadienyl ligands. The advantages of (polypyrazolyl)borates as ligands are as follows: 1) all their salts are soluble in water as well as in organic solvents, are readily prepared, and are stable in air; 2) the ligand $HB(pz)_3^-$ can be synthesized with up to ten substituents, so that steric and electronic relations can be changed as desired whilst retaining the original C_{3v} symmetry of the ligand; 3) the C-protons are excellent symmetry probes, suitable for use in studies of dynamic processes in complexes; and finally 4) for each $R_nB(pz)_{4-n}^-$ ligand there is an isosteric and isoelectronic but neutral ligand $R_nC(pz)_{4-n}$, so that completely analogous metal complexes can be prepared that have a charge greater by +1 per ligand. This is not the case for any other ligand system.

Although these (polypyrazolyl)borates have been known for only a short time they have already proved their value as ligands and further expectations appear certainly justified.

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Reactions on Coordinatively Unsaturated Chromium(II) Surface Compounds

By *Hans-Ludwig Krauss*[*]

For the catalyst of the Phillips polyethylene synthesis it has been shown that the catalytically active centers are coordinatively unsaturated metal ions in a low oxidation state (analogy to the Ziegler-Natta process!)[1]. To assume that these centers constitute a uniform species is, however, too crude a simplification. For silica gel as support, *e.g.*, two kinds of reacting OH groups could be detected; these provide two topologically different points at which Cr^{VI} surface compounds can be formed, this being the first step in the reactions. The existence of two sterically different species has also been proved for the small amounts of Cr^{V} which are obtained as a side product on preparation of the Cr^{VI} surface compounds[2]. After the reduction to Cr^{II}, which then is the coordinately unsaturated surface compound, two different types of Cr^{II} are found again; indeed, by modification of the procedure, one or the other can be made the preponderating, if not the only, species. The products differ in color (green and blue respectively), in their reaction with O_2 (with or without chemiluminescence) and in their behavior towards CO (different IR bands, different stability in vacuum). It is possible that only one of the two species takes part in the polymerization of ethylene.

If the Cr^{II} centers are saturated with strongly bonding ligands, the metal can be removed by protic solvents whilst the ligand-carrier bonds are retained. In this way new complexes can be isolated by reaction of the unsaturated center and subsequent conversion into a homogeneous phase. Especially, on removal from the carrier the bond between the ligand and chromium can be retained when one ligand is a short hydrocarbon chain formed by polymerization of ethylene[3]. Such organochromium compounds are relatively stable in cyclohexane at room temperature in absence of air and protons; they can be sublimed with loss of dipole-bonded ligands (mass spectrum!) and react with a variety of new coordination partners.

Our results provide a first insight into the topology of heterogeneous reactions on amorphous substrates. By removal from the carrier of the coordination compounds formed in this way, a new route is opened for the synthesis of metal complexes.

Lecture at Mülheim (Germany) on May 3, 1973 [VB 372 IE]
German version: Angew. Chem. 85, 921 (1973)

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Reviews

Abstracts of selected progress reports and review articles

Reactions of substituted 1,3,3-trichloro-2-aza-1-propenes are treated by *K. Findeisen, K. Wagner*, and *H. Holtschmidt*. Polychloro-2-aza-1-propenes, and particularly the pentachloro derivative ("trichloromethyl isocyanide dichloride" TMI) are readily accessible by high-temperature chlorination. TMI reacts with carboxamides to give nitriles and with alcohols to give alkyl halides, alkylurethanes, and carbonic esters. Reaction with aldehydes and carboxylic anhydrides affords dichloroalkanes and acyl chlorides respectively. TMI and higher homologs are suitable for the construction of heterocycles, *e.g.* 1,3,5-triazines, pyrimidines, quinazolines, 1,2,4-triazoles, and 1,2,4-oxadiazoles. [Reaktionen der substituierten 1,3,3-Trichloro-2-aza-propene [N-(1,1-Dichloro-alkyl)-imidchloride]. Synthesis *1972*, 599—605; 14 references]

[Rd 617 IE—M]

The use of NMR spectroscopy in studies of organophosphorus compounds is surveyed by *B. I. Ionin* and *T. N. Timofeeva*. The authors systematize the chemical shifts of protons in phosphorus compounds and examine proton-proton and proton-phosphorus interactions. The values obtained serve as basis for a consideration of the nature of the P—H bond. The final section deals with the significance of NMR spectra in structural and conformational analysis of organophosphorus compounds. [Application of Proton Magnetic Resonance to the Investigation of Organophosphorus Compounds. Russ. Chem. Rev. *41*, 390—402 (1972); 167 references]

[Rd 626 IE—Q]

Progress in the chemistry of aliphatic diazo ketones is reviewed by *A. L. Fridman, G. S. Imagilova, U. S. Zahsov*, and *S. S. Novikov*. The article deals with the syntheses available and surveys the literature describing chemical properties. The physical properties and also problems of p-π conjugation and rotational isomerization as well as biological activities are considered in further sections. [Advances in the Chemistry of Aliphatic Diazoketones. Russ. Chem. Rev. *41*, 371—389 (1972); 295 references]

[Rd 627 IE—Q]

The calculation of electronic states of copper(II) complexes by semi-empirical methods is discussed by *D. W. Smith*. A review of spectra measured and assigned up to now is followed by a critical assessment of the models used for interpretation of the spectra. The author recommends the angular overlap model with corrections for electrostatic contributions for the calculation of energy levels in copper(II) compounds. Covalent and electrostatic d-level splitting parameters of the most important ligand atoms are tabulated as functions of the internuclear distance. Using these parameters one should be able to calculate the d-d spectrum of any copper(II) chromophore of known or assumed geometry. [Ligand Field Splittings in Copper(II) Compounds. Struct. Bonding *12*, 49—112 (1972); 197 references]

[Rd 632 IE—H]

Complexes of the platinum metals with molecular oxygen are the topic of a review by *V. J. Choy* and *C. J. O'Connor*. The authors restrict the subject matter to mononuclear complexes with equivalent oxygen atoms occupying two coordination sites of the metal. IR spectra and structural data (bond lengths) are discussed and the metal-oxygen bond is evaluated in terms of MO theory. This is followed by a section on the reaction kinetics of formation (and of dissociation if formation is reversible) of these compounds. Finally, stoichiometric and especially homogeneous catalytic reactions of dioxygen complexes are discussed; they are of considerable importance for our understanding of the function of metalloenzymes. [Chelating Dioxygen Compounds of the Platinum Metals. Coord. Chem. Rev. *9*, 145—170 (1972); 86 references]

[Rd 636 IE—H]

The coordination chemistry of thallium(I) is considered in detail by *A. G. Lee*. The review abounds in tables of physical and physicochemical data, partly comparing Tl(I) with the corresponding alkali compounds. The extensive list of references refers also to work from Russia and eastern Europe. [The Coordination Chemistry of Thallium(I). Coord. Chem. Rev. *8*, 289—349 (1972); 398 references]

[Rd 637 IE—H]

The spin state of pentacoordinate cobalt(II) and nickel(II) complexes depends on the ligand donor atoms and on the complex geometry. This correlation is analyzed by *L. Sacconi*. He shows in an extensive table the connection between the sum of the nucleophilic reactivity constants of the donor atoms and the spin state: a less nucleophilic set of ligands results in high-spin complexes, and a more nucleophilic one in low-spin complexes. Predictions of this type may fail if one metal-donor bond is considerably longer than the remaining four. [The Influence of Geometry and Donor-Atom Set on the Spin State of Five-Coordinate Cobalt(II) and Nickel(II) Complexes. Coord. Chem. Rev. *8*, 351—367 (1972); 117 references]

[Rd 638 IE—H]

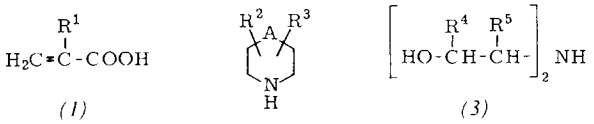
Transition metal complexes of the N^{3-} ligand are the subject of a review by *W. P. Griffith*. A general section dealing with occurrence, stereochemistry, modes of bonding, preparation, and properties of nitrido complexes is followed by a description of the chemistry of the known complexes of this type; high-polymer and most binary nitrides are not covered. Because of its particularly interesting nitride chemistry, mercury is considered here as an "honorary member" of the transition metal group. [Transition Metal Nitrido Complexes. Coord. Chem. Rev. *8*, 369—396 (1972); 100 references]

[Rd 639 IE—H]

Patents

Abstracts of selected "Deutsche Offenlegungsschriften" (DOS), *i. e.* provisionally published specifications as filed with the German Patent Office

Bubble-free polyacrylate castings, which were formerly difficult to produce, are readily obtained by the reaction of monomers having the formula *(1)* with an initiator having the formula *(2)* or *(3)* under a protective gas. The monomer is intimately mixed with the initiator in a reactor and



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

R = alkyl ($C_1 - C_{30}$); R^1 = H, alkyl ($C_1 - C_3$), R^2, R^3 = H, alkyl ($C_1 - C_5$), R^2 and R^3 are attached to different ring C atoms; A = CH_2, O, or NH; R^4, R^5 = H, alkyl ($C_1 - C_3$), R^4 and R^5 are the same or different

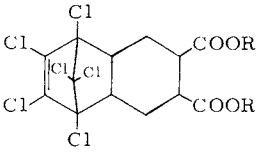
reacts to form a viscous prepolymer, which is then allowed to polymerize to completion without bubbles in stationary conditions. Examples given for initiators having the formula *(2)* are piperidine, morpholine, piperazine, and their alkyl derivatives, while initiators having the formula *(3)* include 2,2'-iminodiethanol, 1,1'-iminodiisopropanol, and similar compounds. Methyl methacrylate is used in particular as the monomer. [DOS 2145289; Texaco Development Corp., New York]

[PR 67 IE—S]

In the low-pressure polymerization of propylene in the gas phase with Ziegler catalysts, a considerable quantity of *n*-heptane-soluble material, which impairs the quality, particularly of injection-molded articles, is usually formed. This fraction can be greatly reduced and subsequent treatment for the removal of catalysts from the final product can be avoided if the catalyst components are brought together before introduction into the reactor under inert gas or under monomer at or slightly above normal pressure, and if the propylene used is so pure that the catalyst yield obtained is more than 10000 parts of polymer/part of heavy metal component and the catalyst activity is higher than 1000 parts of polymer per part of heavy metal component per hour. [DOS 2049623; Badische Anilin- & Soda-Fabrik AG, Ludwigshafen]

[PR 71 IE—T]

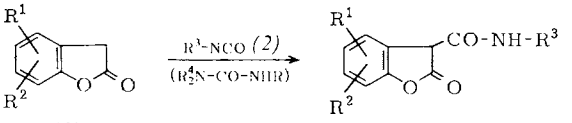
Polymers of allyl esters of hexachlorooctahydromethanonapthalenedicarboxylic acid can be obtained by free-radical polymerization of the compound *(1)*, possibly in combination with a methacrylic ester. The polymerization may be carried out in bulk, in solution, in emulsion, or in aqueous suspension at pressures above or below atmospheric and at temperatures between about 60 and 150 °C. The homo-



polymers and copolymers can be used as potting resins for electrical equipment. [DOS 1770383; Dow Chemical Company, Midland, Michigan]

[PR 82 IE—E]

2-Oxo-2,3-dihydrobenzofuran-3-carboxamides *(3)* and their pharmacologically acceptable salts can be used as anti-inflammatory agents. The compounds *(3)* can be prepared by reaction of 2-oxo-2,3-dihydrobenzofurans *(1)* with



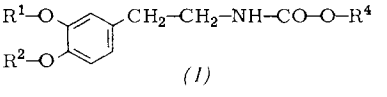
(1) *(3)*

R^1, R^2 = H, F, Cl, Br, CF_3, OCF_3, alkyl (C_1 – C_5), alkoxy (C_1 – C_5); R^3 = naphthyl, (substituted) phenyl, alkyl (C_1 – C_4), alkoxy, alkylthio, CF_3, OCF_3; R^4 = aryl

isocyanates *(2)* or trisubstituted ureas. [DOS 2150901; Pfizer Inc., New York, N.Y.]

[PR 93 IE—N]

Disubstituted *N*-phenethylcarbamic esters *(1)* can be used as antidepressants. They are also suitable for use as active ingredients for long-acting oral antiparkinsonian agents.



(1)

R^1, R^2 = H, (substituted) benzyl, $COOR^3$, $CONHR^3$, $COSR^3$; R^3 = alkyl, alkenyl, alkynyl (C_1–C_5); R^4 = alkyl, alkenyl, alkynyl, haloalkyl, cyclopropylmethyl, 2-(2-furyl)ethyl, cyclobutyl.

[DOS 2160973, Aldrich Chemical Co., Inc., Milwaukee, Wis.]

[PR 104 IE—N]

Progress in Bioorganic Chemistry. Vol. 1. Edited by *E. Kaiser* and *F. Kézdy*. John Wiley & Sons, Inc., New York—London 1971, 1st Edit., ix, 369 pp., numerous figures and tables, £7.—.

The less time a scientist has to consult the primary literature, the greater the importance he will attach to the secondary literature. Handbooks and progress reports give informations on advances in individual fields of science and provide a stepping stone for those wanting to break into new domains. Publishers of secondary literature are therefore assuming a steadily increasing burden of responsibility. "Progress in Bioorganic Chemistry" is the latest newcomer to the field of biochemical secondary literature. The editors understand bioorganic chemistry to be the discipline that has evolved from the interaction between biochemistry and physical organic chemistry. In their view the aim of this new science should be to promote the understanding of biological reactions on the basis of the reaction mechanisms of organic chemistry, in qualitative and quantitative terms, as well as the relationship between the reactivity and structure of the participating molecules, in other words especially catalysts. When we are also told in the Foreword that the chief representatives of this science describe themselves as enzymologists, biochemists, kineticists, and physical organic chemists, then we may conclude that this "new" science fits the old concept of enzymology or enzymatic catalysis, and this domain is hardly new. After all, this year will see the appearance of the 35th volume of "Advances in Enzymology", a series which makes claims similar to those of the new series under discussion, and which, moreover, is brought to us by the same publisher.

On the basis of the first volume it cannot be said that these new progress reports fill a gap. Together with "Advances in Enzymology", "Advances in Catalysis", "The Enzymes", and "The Proteins", they extend the existing series, and hence could in principle extend the information available in the field of enzymology. Do they in fact do so? Regrettably, the answer on the strength of this first volume must be largely no. *Kirby* and *Fersht* devote 82 pages to intramolecular catalysis. The 62-page article by *Bruice* published in "Enzymes" in 1970 deals to a considerable extent with a similar field, and many of the references cited are identical. *Hamilton*'s paper on "The Proton in Biological Redox Reactions" likewise contains material which appeared in the new edition of "Enzymes" or which will do so shortly. The main section of the book, about half, consists of an article by *Coleman* on the role of metal ions in enzymatic catalysis. This field was reported by *Vallee* and *Wacker* a year ago in even greater depth than in the present work ("The Proteins", Volume 5) and by *Mildvan* in the new edition of "Enzymes". (Why does *Coleman* on p. 314 still treat lactate, malate, and glutamate dehydrogenase as zinc enzymes?)

One puts down the first volume of "Progress in Bioorganic Chemistry" with some dissatisfaction. Such extensive overlapping with other progress reports could have been avoided, for the coverage of "Enzymes" and "Proteins" has been known for a long time. This is a poor start for a new series, and the editors will have to seek out more original subjects in order to justify its existence. If they cannot do that, then it would be better to discontinue the series.

Horst Sund [NB 127 IE]

Organophosphorus Chemistry. Vol. 3. Specialist Periodical Reports. Published by The Chemical Society, London 1972. 1st ed., x, 303 pp., bound £ 7.—.

The rapid growth of phosphorus chemistry can be seen from the third volume of "Organophosphorus Chemistry", which covers the literature between July 1970 and June 1971. The publication was again executed under the expert direction of *S. Trippett*, who had the cooperation of eight well-known British specialists as co-authors. 1254 references containing the results of 2055 authors have been taken into account. The division of material that proved successful in the earlier volumes has been retained: Phosphines and Phosphonium Salts (*D. J. H. Smith*, 29 pp.); Pentavalent Phosphorus Compounds (*S. Trippett*, 11 pp.); Halophosphines and Related Compounds (*J. A. Miller*, 13 pp.); Phosphine Oxides and Phosphine Sulfides (*J. A. Miller*, 14 pp.); Acids of Trivalent Phosphorus (*B. J. Walker*, 29 pp.); Acids of Pentavalent Phosphorus (*N. K. Hamer*, 27 pp.); Phosphates and Phosphonates of Biochemical Interest (*D. W. Hutchinson*, 28 pp.); Ylides and Related Compounds (*S. Trippett*, 37 pp.); Phosphazenes (*R. Keat*, 39 pp.); Free-Radical, Photochemical, and Deoxygenation Reactions (*R. S. Davidson*, 18 pp.); Physical Methods (*J. C. Tebby*, 45 pp.).

The value of this series of books for many preparative and also biochemical laboratories can therefore scarcely be overrated, since despite strenuous efforts, the new edition of "Kosolapoff" is constantly falling behind schedule and the series "Topics in Phosphorus Chemistry" has ceased publication.

The third volume of "Organophosphorus Chemistry", like its predecessors, makes a good impression in every respect, and can be recommended to all interested specialists.

Leopold Horner [NB 129 IE]

The Nuclear Overhauser Effect—Chemical Applications. By *J. H. Noggle* and *R. E. Schirmer*. Academic Press, New York—London 1971. 1st ed., xi, 259 pp., numerous figures and tables, bound $ 14.50.

Nearly all the textbooks on high-resolution magnetic NMR spectroscopy that have appeared in recent years and are suitable for chemists provide insufficient information on spin-lattice relaxation and the closely related nuclear Overhauser effect (NOE). Until now there has been no synopsis that both deals with the theory at a middle level and clearly shows the possibilities and limitations of the method.

This gap has now been bridged by the present monograph. A concise, clear introduction to spin-lattice relaxation by consideration of population differences and transition probabilities and an explanation of the relaxation times are followed by the derivation of the Solomon equation. Contrary to their expressed aim, the authors were evidently unable at this point to avoid referring to *Abragam*'s "Principles of Nuclear Magnetism" at the start of the calculation.

Further mainly theoretical chapters deal with the mechanisms of spin-lattice relaxation, the fundamentals of the determination of internuclear distances, and conformational analysis with the aid of the NOE. A number of sections in Chapter 5 (Experimental Methods), could,

in the review's opinion, have been omitted; examples are the sections on side-band technique, modulation, and frequency field stabilization. A clear delimitation of the term "nuclear Overhauser effect", which the authors unfortunately omit, would also have led to the exclusion of Chapter 7, which describes the application of the double resonance method to dynamic processes.

On the other hand, the reader is bound to be pleased with the extremely carefully compiled, remarkably comprehensive literature survey, which takes into account articles up to December 1970. The author does not shrink from harsh criticism in discussing the results of investigations. A comprehensive bibliography is appended.

It is to be hoped that this book will not be read exclusively by specialists. It has valuable suggestions for the preparative chemist, particularly in the field of natural products, even if he ignores the greater part of the theoretical chapters.

Wolfgang Herrig [NB 132 IE]

Analytical Photochemistry and Photochemical Analysis. Edited by *J. M. Fitzgerald*. Marcel Dekker, Inc., New York 1971. 1st ed., xiv, 360 pp., 49 figs., bound $ 23.50.

The editor, who is himself the author of Chapter 5 (Photochemical Titrations), attempts to interest both photochemists and analysts in a total of nine contributions of different lengths (11–87 pp.). The division of the subject matter has been carried out accordingly.

The first section (three chapters totalling 112 pp.) first presents general information on photochemical methods; however, the list of companies is only of limited value to the European reader. Chapter 2 then deals very concisely and clearly with lasers (theory and construction principles) and their use in Raman and emission spectroscopy among other things. The list of actinometers in Chapter 3 will be welcomed by the experimental photochemist.

The second section deals with photochemical reactions in analytical chemistry. Two chapters describe the determination of mostly inorganic substances *e.g.* by photochemical titrations, in which the reaction of a substance with photons is followed directly or by means of a photochemically produced reagent, usually with spectrophotometric determination of the end point. This section, with a length of 46 pages, is the shortest, but points to the relatively new links between photochemistry and analytical chemistry.

The third section (four chapters, 168 pp.), on analytical methods in photochemistry, is concerned not with the use of conventional analytical methods for the identification of products but with the detection of the reactive states and of short-lived intermediates. Chapter 6 deals with "radical scavenging", triplet energy transfer, matrix spectroscopy and other spectroscopic techniques. A notable omission here is the absence of any reference to CIDNP. Flash spectroscopy is also discussed, though the whole of Chapter 7 is also devoted to this subject. This overlap could have been avoided; a method as important as this deserves a self-contained treatment. The last two chapters are very special; the short chapter on analysis for coordination compounds in the solid state could have been safely omitted. On the other hand, a separate chapter on methods for the investigation of the light sensitivity of polymers would not have been out of place, in view of the practical importance of plastics.

The subject and author indexes, unlike the figures, are adequate. The book can be recommended only with reservations; it will be of advantage only to the photochemist who can make the correct selections from the 900 references.

D. Rehm [NB 142 IE]

Far-Infrared. By *K. D. Möller* and *W. G. Rothschild*. John Wiley and Sons, New York 1971. 1st ed., xix, 797 pp., numerous figures and tables, bound £ 15.25.

The aim of the book is to provide information on the research possibilities and recent developments of far-infrared (FIR) spectroscopy in the fields of physics, chemistry, and biochemistry. The chemist has learned to make correct use of many physical measuring instruments, even though he regards them only as "black boxes". For the use of FIR spectroscopy, however, he still needs information about the physical principles of the measuring instruments and of the measuring process. It is therefore gratifying to find that the present book deals first, in four chapters, with the properties of grating spectrometers, interferometers and their components, and the principles of Fourier transform spectroscopy. The principal chemical applications of FIR spectroscopy are discussed in the next four chapters; these are low-frequency stretching and deformation vibrations, FIR spectra of systems bonded by hydrogen bonds, skeletal vibrations of strained ring systems, and torsional vibrations with a periodic potential barrier. These are followed by chapters on the pure rotation spectrum of water, collision-induced spectra at long wavelengths, rotational-translational movements in condensed phases, the FIR spectra of diatomic cubic crystals, and the FIR spectra of polyatomic crystals. In six appendices, specialists present reports on defect-induced lattice absorption in the far-infrared, dielectric properties and optical phonons in paraelectric and ferroelectric perovskites, magnetic phenomena in the far-infrared, FIR-spectroscopic studies on semiconductors, superconductivity, and rapid Fourier spectroscopy. A bibliography covering the entire literature on FIR spectroscopy from 1892 to 1969, with 1512 references, completes this useful book, which provides detailed information from the many possible fields of chemistry and physics. There are few spectroscopic methods for which such a comprehensive book can be written today.

Bernhard Schrader [NB 145 IE]

Statistische Auswertungsmethoden (Statistical Evaluation Methods). By *L. Sachs*. Springer-Verlag, Berlin–Heidelberg–New York 1972. 3rd revised and expanded edition, 548 pp., 59 figs., bound DM 58.—.

The fact that new editions have been necessary at intervals of two years after the first edition in 1967 shows that the author has succeeded in producing an account of statistical evaluation methods that appeals to and satisfies a wide readership. The third edition, which is slightly larger than the second edition, again contains a description, in seven sections, of a large number of statistical approaches and procedures that have proved useful in practice, without abstract mathematical derivations and proofs. After preliminary remarks with an introduction to the elementary principles of a rational arithmetic, the first section deals with the groundwork for statistical decision-making techniques, such as the elements of probability calculations, and

the types of distribution function. After the description of applications in medicine and technology, there are two sections on simple comparison tests and other special test procedures. The large number of tests mentioned presents a hidden danger of different interpretations and judgements for the same fundamental data if the test used is left to the observer's discretion. A more detailed discussion of the conditions and reliability criteria would therefore have been advisable in places. The presentation of the methods of correlation and regression analysis, the evaluation of multi-field tables, and variance analysis in the following sections is extremely good. The material is made very understandable even to readers with little mathematical knowledge by 400 numerical examples, 59 exercises (with solutions in the appendix), and more than 210 tables. It will also be a valuable textbook and reference book in the future for readers concerned mainly with applications.

Günter Gottschalk [NB 148 IE]

Physical Chemistry—An Advanced Treatise. Vol. VIIIB. Liquid State. By *H. Eyring, D. Henderson*, and *W. Jost*. Academic Press, New York—London 1971. 1st ed., xix, pp. 413–892, numerous figures, bound $ 25.—.

The present part completes the eight volume of this compilation, which may almost be described as encyclopedic. The conception of the work cannot be too highly praised. For a comprehensive and at the same time up-to-date account of the entire field of physical chemistry, it is essential that the various chapters should be entrusted to specialists. The work as a whole must then be judged both on the quality of the individual chapters and on the degree to which the editor has succeeded in imparting unity to the work.

The present part begins with a chapter on liquid mixtures (*D. Henderson* and *P. J. Leonard*). After a brief discussion of the mixing rules known for intermolecular potentials, simple cases (one-dimensional systems, systems consisting of hard spheres and of molecules with Lennard-Jones interaction) are dealt with; the principal theories are presented in detail (quasi-lattice theory of *Guggenheim-Percus-Yevick*, perturbation theories from *van der Waals* to *Leonard-Henderson-Barker*, "n-fluid" theories), and their results are critically compared. The chapter on liquid helium (*D. ter Haar*) contains a very readable description of the theories for ^{3}He and ^{4}He. If we complain that too little space is devoted to the description of the properties of liquid helium, it is only because slightly more would have allowed a completeness that is desirable above all on didactic grounds.

The chapter on the time-dependent properties of condensed media (*B. J. Berne*) is rightly the largest chapter in the present volume. In addition to the consequences of the linear response theory (magnetic susceptibility, width of spectral lines, relaxation time), the properties of correlation functions and memory functions are discussed in detail. The section on computer experiments is too short and tells the reader nothing that he would not already know if he had worked through the book up to this point. The section on molecular orientations in gases and liquids, on the other hand, contains all the important information on experimental and theoretical methods for the study of molecular motions.

Two chapters on critical phenomena follow. *J. Stephenson* deals with the static aspects, and the chapter on dynamic critical phenomena was written by *H. E. Stanley, G. Paul*, and *S. Milošević*. *Stephenson* more than the other authors has allowed himself to be guided by didactic motives. The fundamentals of the theory are described almost without prior assumptions, and an eye-catching weight of face has been used for fundamental facts.

The present volume does what it promises. In every chapter the reader receives concise but comprehensive information on the topic discussed. The circle of readers who will be interested in this volume is naturally small. It will appeal to all physical chemists who are interested both in theoretical and in experimental methods for the study of liquids.

Arno Höpfner [NB 156 IE]

Messergebnisse und ihre Auswertung. (Experimental Results and their Evaluation). An introduction to practical work in natural science. By *G. L. Squires*. Walter de Gruyter, Berlin—New York 1971. 1st ed., 240 pp., 77 figs., bound DM 29.—.

The book is divided into three parts: "Statistical Treatment of Experimental Data", "Experimental Methods", and "Records and Calculations". A survey of the calculation and estimation of errors is given in the first part, while the second part (which is better described by its original title "Practical Physics" than by the German title) shows with the aid of selected samples the errors that can creep into an experiment and how these errors can be avoided; the third part contains hints on how experimental results should be recorded, evaluated and presented.

These topics are dealt with in an unusually original manner (*e.g.* chapter headings "Common Sense and Errors", "Logic in Experimenting", "Common Sense in Experiments"). No consideration is presented without an example (and these examples are excellently chosen) to bring out the essential point.

The book can be warmly recommended to all students of natural sciences, mainly as supplementary reading to practical exercises. However, the many Anglicisms that have crept into the German text (and these are very disturbing in places) should be eliminated in a new edition.

H.-D. Försterling [NB 169 IE]

Mathematik für Chemiker (Mathematics for Chemists). By *H. G. Zachmann*. Verlag Chemie GmbH., Weinheim/Bergstrasse 1972. 1st Edit., xvi, 593 pp., bound DM 64.—.

For the study of chemistry in the narrow sense, only a relatively modest mathematical background is expected of the student, at least in the early stages. Later in the course, as he becomes increasingly concerned with physico-chemical problems, much greater demands are very soon placed on the student's mathematical knowledge and skills. This is particularly true of students who intend to prepare a degree or doctorate thesis on a physico-chemical topic. As a result of the increasing use of physico-chemical methods in chemistry as a whole, however, other chemists must generally also have a well-grounded mathematical training designed to meet the special requirements of chemical applications.

There is no doubt that until recently, a great deal of experiment and improvisation has gone into the mathematical instruction of chemists. On the one hand, the courses designed primarily for mathematicians are often too narrow

in their scope or too demanding; on the other hand, a one-semester course on infinitesimal calculus of greatly reduced content (*e.g.* given by assistant lecturers on the university staff), possibly with the addition of a few references to other important fields of practical mathematics, is no longer adequate in view of the requirements mentioned. A similar situation is found in the German-language textbooks available until recently in this field. The earlier mathematics textbooks for chemists no longer covered the entire field of practical mathematics that should be mastered by the chemist. The compendia compiled for use in physics and chemistry are mainly of the nature of reference works, whose use calls for some existing background knowledge.

Since the chemistry student is faced with mathematical problems mainly in physical chemistry, some universities have experimented successfully with leaving the mathematical instruction of chemists to a lecturer from the field of physical chemistry. The present work is also based on courses for chemistry students at the University of Mainz. The well laid out book deals lucidly with the entire field of classical practical mathematics that is important nowadays for the treatment of chemical or physico-chemical problems. The mathematical formalism is clearly illustrated in every case by concrete examples, and the reader can check the state of his own knowledge by means of test questions and exercises incorporated into the text.

In addition to infinitesimal calculus and linear algebra, the fields of probability calculus, statistics, and group-theory, which are at least equally important to the chemist, are also dealt with. From his own experience of mathematics courses for chemists, the reviewer feels that a definite need has been filled by the publication of this book. Though the book almost attains the proportions of a reference work in some sections, it nevertheless makes an excellent impression on the whole. It should therefore always be used as an aid in the preparation of mathematics courses for chemists, and its purchase in fairly large numbers can be recommended to the libraries of institutes and training colleges. The high price is regrettable, and will undoubtedly place the book beyond the pockets of many chemistry students who would otherwise be interested.

Theodor Ackermann [NB 171 IE]

Recent Books

The following books have been received by the editor. Detailed reviews will not be published in all cases because of the limited space available under this heading in the journal.

Short Course in Biochemistry. By *A. L. Lehninger*. Worth Publishers, New York 1973. xliv, 420 pp., bound \$12.50.

Contents: Biomolecules; Catabolism and the Generation of Phosphate-Bond Energy; Biosynthesis and the Utilization of Phosphate-Bond Energy; Replication, Transcription, and Translation of Genetic Information.

Progress in Organic Chemistry, Vol. 8. Edited by *W. Carruthers* and *J. K. Sutherland*. Butterworths, London 1973. vii, 343 pp., bound £ 9.50.

Contents: Synthesis of Prostaglandins; Biogenetic-Type Synthesis of Terpenes; Advances in the Chemistry of Cannabinoids; Penicillin Chemistry; Advances in the Chemistry of Cyclic Peptides; Chemiluminescence of Organic Compounds; Recent Work on Nitration; Homogeneously Catalysed Hydrogenation.

Analytical Chemistry of Selenium and Tellurium. By *I. I. Nazarenko* and *A. N. Ermakov*. From the series "Analytical Chemistry of the Elements". Halsted Press, a division of John Wiley & Sons, Inc., New York 1973. x, 281 pp., bound £ 9.35.

Contents: Chemical and Analytical Characteristics of Selenium and Tellurium and Their Compounds; Qualitative Detection of Selenium and Tellurium; Quantitative Determination of Selenium and Tellurium; Methods for Separating Selenium and Tellurium from Foreign Elements; Determination of Selenium and Tellurium in Natural and Industrial Substances; Determination of Impurities in High-Purity Selenium and Tellurium.

Pesticide Formulations. Edited by *W. van Valkenburg*. Marcel Dekker, Inc., New York 1973. x, 481 pp., bound \$ 29.50.

Contents: Correlation of Biological Activity with Chemical Structure and Physical Properties; The Emulsifier; The Stability of Emulsions; Agricultural Formulations with Liquid Fertilizers; Formulation of Pesticidal Dusts, Wettable Powders and Granules; Plant for the Formulations of Insecticides; Reducing Pesticide Chemical Drift; Spreading and Retention of Agricultural Sprays on Foliage; Penetration and Translocation of Herbicides; Adsorption, Movement, and Distribution of Pesticides in Soils.

Mathematical Methods for Chemists. By *R. K. Mackie, T. M. Shepherd*, and *C. A. Vincent*. The English Universities Press, London 1972. v, 154 pp., bound £ 2.95 (Boards Edition); £ 1.65 (Unibook Edition).

Contents: Functions and Operations; Differential Calculus; Integral Calculus; Differential Equations; Coordinate Systems; Complex Numbers; Vector Analysis; Determinants and Matrices; Expansion of Functions; Statistical Methods; Graphical Methods; Basis Equations; Derivatives; Standard Integrals; Laplace Transforms; Solution of Polynomial Equations.

Analytical Profiles of Drug Substances, Vol. 2. Edited by *K. Florey*. Academic Press, New York, London 1973. xi, 575 pp., bound \$ 18.50.

Contents: Ampicillin; Chlorprothixene; Chloral Hydrate; Clidinium Bromide; Dexamethasone; Dioctyl Sodium Sulfosuccinate; Fluorouracil; Fluphenazine Enanthate; Fluphenazine Hydrochloride; Isocarboxazide; Isopropamide; Levallorphan Tartrate; Methyprylon; Phenelzine Sulfate; Primidone; Propiomazine Hydrochloride; Sulfamethoxazole; Sulfisoxazole; Triclobisonium Chloride; Trifluopromazine Hydrochloride; Trimethobenzamide Hydrochloride.

The Chemistry of Enamines. By *S. F. Dyke*. Cambridge University Press 1973. vii, 93 pp., stitched £ 1.40/bound £ 2.90.

Contents: Preparation and Some Properties; Reactions; Heterocyclic Enamines.

Electrophilic Substitution at a Saturated Carbon Atom. Vol. 12 of the series "Comprehensive Chemical Kinetics". Edited by *C. H. Bamford* and *C. F. H. Tipper*. Elsevier Scientific Publishing Company, Amsterdam, London, New York 1972. xiii, 256 pp., bound Dfl. 90.00/$ 31.60.

Contents: The Formation and Reactions of Carbanions; Mechanisms of Electrophilic Substitution at Saturated Carbon; The Unimolecular Mechanism, SE1.5; Mercury-for-Mercury Exchanges; Other Metal-for-Metal Exchanges; Acidolysis of Organometallic Compounds; Halogenolysis.

The Electronic Structure of Molecules: Theory and Application to Inorganic Molecules. By *G. Doggett*. Vol. 3 of the series "The International Encyclopedia of Physical Chemistry and Chemical Physics", Topic 4: Electronic Structure of Molecules. Edited by *J. W. Linnett*. Pergamon Press, Oxford, New York, Toronto, Sydney, Braunschweig 1972. xiv, 172 pp., bound £ 5.75.

Contents: Orbital Theories of Electronic Structure; The Electronic Structure of Some Molecules Containing a Central Second-Row Atom; The Electronic Structure of Transition Metal Ion Complexes; The Electronic Structure of Xenon Fluorides; Calculation of the Diagonal Matrix Element of the Molecular Electronic Hamiltonian for a Wave Function Given as an Antisymmetrized Product of One-Electron Functions (not necessarily Orthogonal); Character Tables for O_h and T_d Point Groups; Symmetry Adapted Combinations of Atomic Orbitals for an Octahedral Molecule (Point Group O_h).

Chemistry and Biology of Peptides. Edited by *J. Meienhofer*. Ann Arbor Science Publishers, Ann Arbor 1972. xxi, 762 pp., bound £ 11.00.—Proceedings of the Third American Peptide Symposium.

Säuren und Basen (Acids and Bases). By *F. Dietze, E. Hoyer, F. Lorenz, W. Seifert*, and *D. Wagler*. Verlag Chemie, Weinheim 1972. 106 pp., stitched DM 13.80.—Chemie-Programm—ein Lehrprogramm für Hochschulen.

Lehrsystem Elektronik. (Electronics Teaching System). By *G. Markesjö*. Part A: Analog Technology—Experimental and Problem Volume. Verlag Chemie, Weinheim—Carl Hanser Verlag, Munich 1973, 67 pp., stitched DM 24.80.

Contents: Oscillograph; Semiconductor Components; Simple Amplifier Stages; Differential Amplifiers; Solutions and Methods for the Preparation Problems.

An Introduction to Macromolecules. By *L. Mandelkern*. Vol. 17 of the series "Heidelberg Science Library". Springer-Verlag, Berlin, Heidelberg, New York 1972. xi, 161 pp., stitched DM 18.60/$ 5.90.

Contents: Structural Features and Preparation; Chain Structure; Rubbers and Glasses; Crystalline Polymers and Fibers; Macromolecules of Biological Importance; Macromolecules and Man.

Vom Wasser. Ein Jahrbuch für Wasserchemie und Wasserreinigungstechnik. Band 39. (On Water. A Yearbook for Water Chemistry and Water Purification Technology. Vol. 39). Edited by the Water Chemistry Group of the Gesellschaft Deutscher Chemiker. Editor responsible for text: *W. Husmann*. Verlag Chemie, Weinheim 1972. xii, 393, 133 pp., bound DM 68.—.

Schutz gegen atmosphärische Korrosion. Theorie und Technik. (Protection against Atmospheric Corrosion. Theory and Technology). By *K. Barton*. Verlag Chemie, Weinheim 1973. x, 209 pp., bound DM 65.—.

Contents: Introduction; The Atmosphere as a Corrosive Environment; Mechanism and Kinetics of Atmospheric Corrosion; Nonuniform and Structural Corrosion Phenomena; Principles of Protection against Atmospheric Corrosion; Principles of Methods for the Study of Effects of Atmospheric Corrosion; Outline of Technical and Economic Considerations in Protection against Atmospheric Corrosion.

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Oxathiazinone Dioxides—A New Group of Sweetening Agents

By Karl Clauss and Harald Jensen[*]

Dedicated to Professor Werner Schultheis on the occasion of his 70th birthday

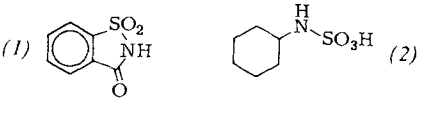
1,2,3-Oxathiazin-4(3*H*)-one 2,2-dioxides bearing lower alkyl substituents on C-5 and C-6 represent potential sweeteners. They are formed from chloro- or fluorosulfonyl isocyanate and acetylenes, ketones, β-diketones, β-oxo carboxylic esters, or benzyl vinyl ethers *via* *N*-halosulfonyl β-oxo carboxamides as common intermediates.

1. Introduction

Since time immemorial the sensation of sweetness of a fruit, a plant secretion, or honey has provided man—and probably also other animals—with a principle for the selection of suitable nourishment from the fullness of his environment. In the course of cultural development, sweet natural products were employed in the preparation of food to intentionally modify its taste. Thus began the checkered history of the development of sweeteners, starting with the domestication of the honeybee and continuing through to the migration of sugar cane from Indochina, *via* the Mediterranean, to America. Cane sugar was unknown in Central Europe until the time of the Crusades. Here the reader is reminded of the introduction of sugar beet cultivation during the Continental Blockade. Cane and beet sugar have remained the dominant sweetening agents since the foundation of the sugar industry and annual production now runs at some 75 million tonnes. This figure testifies to man's love of sweetness.

The high sugar consumption in developed countries whose populations are plagued by such civilization diseases as diabetes, hyperlipemia, obesity, cardiac infarction, caries, or gout is attracting increasing attention from physicians and nutritionalists. Thus the search for sweeteners which do not overtax the metabolism even on liberal comsumption, *i.e.* low-calorie sweeteners, has become more pressing than ever. The sugar substitutes sorbitol or fructose long used by diabetics are metabolized slowly but nevertheless completely and therefore offer no solution to the problem of low-calorie sweetening, especially since their sweetening power is no greater than that of sugar.

Anybody having to live on a diet or wishing to consume less sugar without foregoing sweetness must take recourse to a "synthetic sweetener" in the narrow sense of the term. Such agents cover a whole variety of compounds, the only real limitation being that they should be several orders of magnitude sweeter than saccharose. Many such compounds have been discovered largely by chance during the past hundred years[1]. For toxicological reasons, however, only two were permitted for general use as sweeteners until quite recently: saccharin *(1)* and cyclamate *(2)* in



the form of their neutral sodium and calcium salts. Saccharin is 100 to 500 times as sweet as saccharose, and cyclamate 30 times as sweet.

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Like most synthetic sweeteners, the well-established saccharin, which was discovered in 1879, suffers from a bitter metallic aftertaste. Only cyclamate, which was introduced as a sweetener in 1950, is characterized by an almost pure sweet taste and its triumphal conquest of the sweetener market was therefore without parallel. Its success story came to a grinding halt when it was found to be partially metabolized to the carcinogen cyclohexylamine[2,3] in humans and to cause bladder cancer in rats[4]. Its use was finally banned in the USA and many other industrial countries in 1970. Almost simultaneously it was discovered that saccharin can also give rise to bladder cancer[5]. The Food and Drug Administration of the USA accordingly removed saccharin from their GRAS (Generally Recognized as Safe) list, a collection of about 1000 chemicals generally considered to have no harmful action. The toxicity of saccharin is now being studied on a world-wide basis and the results obtained may also lead to its being banned.

The intensive search for new low-calorie and toxicologically safe sweeteners can be readily appreciated against this background.

This search is still confined to the heuristic principle. There are general theories on the correlation of structure and sweetness[6-8] but they are hardly suited as a basis for a directed search for new sweeteners. Consequently, a checkered mixture of compounds whose sweet taste was discovered by accident has accumulated in recent years[9]. Their suitability as sweeteners has been studied in some cases and one of them, L-aspartyl-L-phenylalanine methyl ester[10], developed jointly by G. D. Searle Co. and Ajinomoto Co. Inc., has good prospects of official acceptance.

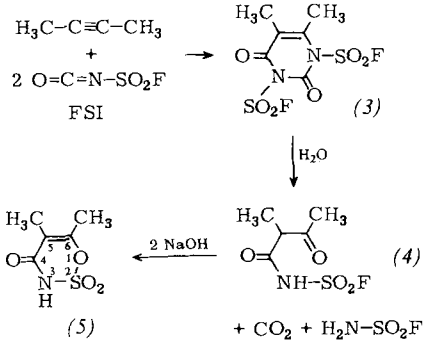
No definite regulations exist as to which stipulations of the licensing authorities must be fulfilled by a sweetener in order to be released onto the market. The situation differs from that of a pharmaceutical preparation in that a sweetener is ingested regularly for long periods and consequently requires more rigorous toxicological testing. In particular, long-term feeding experiments on several animal species and studies on possible carcinogenic, mutagenic, and teratogenic effects and on its metabolism are necessary. Moreover, a sweetener must be water-soluble and within certain limits stable to hydrolysis, *i.e.* resistant to boiling and baking, and be devoid of any aftertaste.

The human tongue is especially sensitive to fine differences in the sweet regime, such as the differences in taste between the isomeric hexoses and disaccharides, and to the presence of aftertastes. Nevertheless, it is difficult to determine how many times sweeter a sweetener is than the reference substance saccharose. Relative sweetness is measured by establishing which of a series of sugar solutions of various concentrations is just as sweet as a sweetener solution of known concentration. Since differing sensations of taste are generally being compared in such tests a certain degree of inaccuracy cannot be avoided. Moreover, the complicated[30,31] dependence of the intensity of a given taste upon concentration permits recognition of only relatively large concentration differences. However, tests on a large number of human subjects and statistical evaluation of the results do lead to reliable data[11]. The measurements show that the relative sweetness does not display a corresponding increase with rising concentration. Thus saccharin is 500 times sweeter than a 1.2% saccharose solution but only 100 times sweeter than a 8.5% saccharose solution. Apart from toxicological considerations, the organoleptic properties mainly decide the usefulness of a sweetener.

2. The FSI Method

2.1. Acetylenes

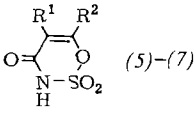
The above situation in the field of sweeteners was responsible for our interest when we encountered a sweet-tasting compound on reaction of 2-butyne with fluorosulfonyl isocyanate (FSI). The reaction[12] proceeds according to Scheme 1.



Scheme 1.

2-Butyne reacts with FSI to give bis(fluorosulfonyl)uracil *(3)*, whose structure was confirmed by X-ray analysis[13]. Hydrolysis of this compound leads to *N*-fluorosulfonyl-α-methylacetoacetamide *(4)* which undergoes surprisingly smooth ring closure to give the new heterocycle 5,6-dimethyl-1,2,3-oxathiazin-4(3*H*)-one 2,2-dioxide *(5)* under the action of sodium hydroxide solution. Other alkynes such as 1-butyne or 1-hexyne undergo analogous reactions *via* uracil derivatives to the 6-alkyl derivatives *(6)* and *(7)* which also have a sweet taste (Table 1).

Table 1. Oxathiazinone dioxides from alkynes.



(5)–(7)

Cpd.	R^1	R^2	Starting material	Yield [%]	M.p. [°C]
(5)	CH_3	CH_3	2-butyne	75	108.5
(6)	H	C_2H_5	1-butyne	8	80
(7)	H	n-C_4H_9	1-hexyne	14	63

N-Fluorosulfonyl β-oxo carboxamides, *e.g. (4)*, proved to be essential intermediates for the formation of the new oxathiazinone system. A broader-based study of the sweeteners required development of a simpler preparation for these intermediates that would also permit variation of the substituents.

2.2. Ketones

Reaction of α-unsubstituted ketones with FSI was recognized as an important general method of preparing *N*-fluorosulfonyl β-oxo carboxamides[14]. Ketones of this kind generally react with halosulfonyl isocyanates with replacement of an α hydrogen atom[15]. In some cases the resulting sulfonyl fluorides *(8)* are obtained in crystalline form (Table 2)[*].

Table 2. *N*-Fluorosulfonyl β-oxo carboxamides *(8)*.

Cpd.	R^1	R^2	Starting ketone	Yield [%]	M.p. [°C]
(8a)	CH_3	CH_3	2-butanone	77	45
(8b)	$-(CH_2)_4-$		cyclohexanone	65	91
(8c)	$-o\text{-}C_6H_4-(CH_2)_2-$		α-tetralone	82	133

No isolation or purification of this precursor is necessary since ring closure also occurs with the crude products and the pronounced tendency of the oxathiazinone dioxides *(9)* to crystallize renders their purification simple. The route afforded the products listed in Table 3.

$$R^1\text{–}CH_2\text{–}CO\text{–}R^2 + O{=}C{=}N\text{–}SO_2F \xrightarrow[\text{FSI}]{}$$

(8) → *(9)*

Table 3. Oxathiazinone dioxides *(9)* obtained from ketones.

Cpd.	R^1	R^2	Starting ketone	Yield [%]	M.p. [°C]	Sweetness
(9a)	H	CH_3	acetone	13	123.5	+
(5)	CH_3	CH_3	2-butanone	45	108.5	+
(9b)	CH_3	C_2H_5	3-pentanone	60	94	+
(9c)	C_2H_5	CH_3	2-pentanone	55	102	+
(9d)	$n\text{-}C_3H_7$	CH_3	2-hexanone	50	96.5	+
(9e)	$i\text{-}C_3H_7$	CH_3	4-methyl-2-pentanone	35	114	+
(9f)	$-(CH_2)_4-$		cyclohexanone	60	123	
(9g)	C_2H_5	$n\text{-}C_3H_7$	4-heptanone	43	86	+
(9h)	H	C_6H_5	acetophenone	9	181	
(9i)	$n\text{-}C_3H_7$	$n\text{-}C_4H_9$	5-nonanone	49	47	
(9j)	CH_3	C_6H_5	propiophenone	63	123	
(9k)	C_6H_5	CH_3	phenylacetone	67	145	
(9l)	$-o\text{-}C_6H_4-(CH_2)_2-$		α-tetralone	76	216	
(9m)	$n\text{-}C_8H_{17}$	CH_3	2-undecanone	50	58	
(9n)	$n\text{-}C_4H_9$	$n\text{-}C_5H_{11}$	6-undecanone	43	35	

Homogeneous reaction products are obtained from symmetrical dialkyl ketones or from ketones bearing no α-hydrogen on one side. Ketones exhibiting sufficiently different activation of the α-hydrogens, *e.g.* methyl alkyl ketones or methyl benzyl ketones, react regiospecifically.

Ketones offering only a methyl as point of attack by FSI, *e.g.* acetone or acetophenone, react only with difficulty and yield mainly side products. A more productive route was therefore sought for preparing the 6-methyl derivative *(9a)*.

[*] *N*-Fluorosulfonyl-α,α-dimethylacetoacetamide [15] can also readily be obtained in crystalline form from methyl isopropyl ketone and FSI but the absence of a proton necessary for enolization prohibits its cyclization to oxathiazinone dioxide.

2.3. β-Diketones

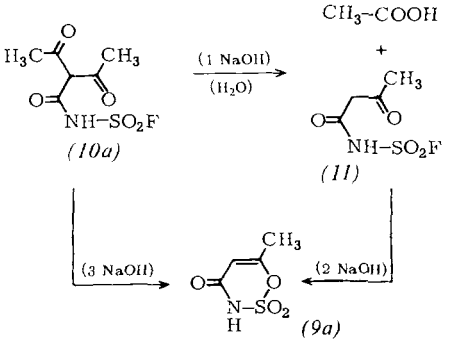
The activated methylene group of β-diketones is attacked particularly readily by FSI to give *N*-fluorosulfonyl diacylacetamides *(10)*[15].

$$R^1\text{–}CO\text{–}CH_2\text{–}CO\text{–}R^2 + O{=}C{=}N\text{–}SO_2F \xrightarrow[\text{FSI}]{}$$

(10)

These products are shown by their ^{1}H-NMR spectrum in solution to exist as the enols and to be strongly chelated ($\delta = 13.5$ and 16 ppm). The yields are very good, *e.g.* almost quantitative for acetylacetone. The *N*-fluorosulfonyldiacylacetamides *(10)* lose an acyl group on heating with ethanol or on stirring with 1 mol of aqueous alkali and thus furnish *N*-fluorosulfonyl β-oxo carboxamides [*(11)*, 75% yield] especially smoothly: the latter then cyclize to oxathiazinone dioxide with more alkali. There is no need to isolate the intermediate since addition of 3 mol of alkali effects both release of the acyl group and ring closure to give, *e.g.* 6-methyloxathiazinone dioxide *(9a)* in 80% yield.

Benzoylacetone and dibenzoylmethane react in a corresponding manner: mild deacylation readily yields the *N*-



fluorosulfonylbenzoylacetamide *(12)* whose ring closure affords 6-phenyloxathiazinone dioxide *(9h)*. A new variant

occurs if *N*-fluorosulfonyl-α-benzoylacetoacetamide *(10b)* is cyclized directly with 3 mol of sodium hydroxide solution. In this case only partial removal of the acetyl group occurs and the 5-acetyl-6-phenyl derivative *(9o)* results (Table 4).

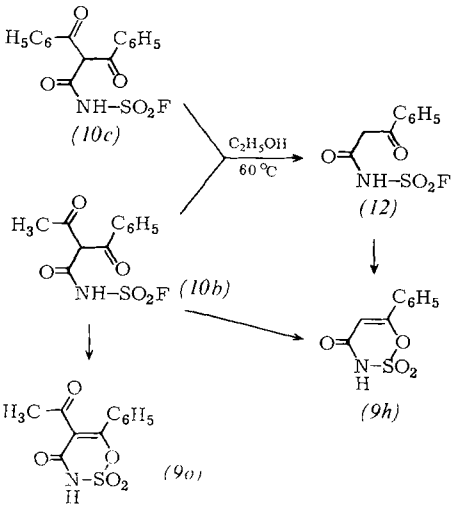


Table 4. Oxathiazinone dioxides from β-diketones.

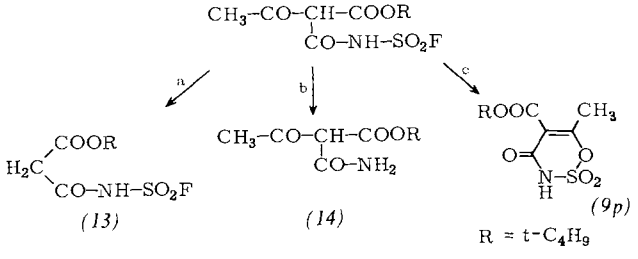
Cpd.	R^1	R^2	Starting material	M.p. [°C]
(9a)	H	CH_3	acetylacetone	123.5
(9h)	H	C_6H_5	benzoylacetone, dibenzoylmethane	181
(9o)	$CO-CH_3$	C_6H_5	benzoylacetone	164

2.4. β-Oxo Carboxylic Acid Derivatives

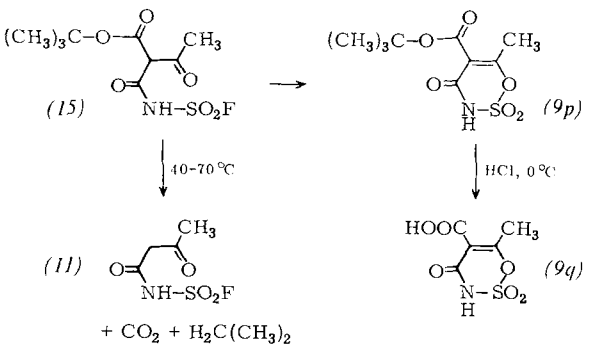
Free β-oxo carboxylic acids such as acetoacetic acid react with FSI with elimination of CO_2 to give *N*-fluorosulfonylamides *(11)*. Owing to the well-known lability of β-oxo acids this reaction has no practical importance.

The α-substitution products[15] of acetoacetic esters and FSI react in various ways on treatment with alkalis. Several parallel reactions occur and lead:

a) to malonic ester derivatives *(13)* by deacetylation;
b) to amides *(14)* by elimination of the SO_2F group;
c) to ring closure in the case of the *tert*-butyl ester.



tert-Butyl acetoacetate reacts with FSI to give a thermolabile α-substitution product *(15)*, m.p. 53 °C, 97% yield, from which a 37% yield of the oxathiazinone *(9p)* can be obtained by ring closure. Acid cleavage of the ester group with hydrogen chloride furnishes oxodihydrooxathiazine-5-carboxylic acid dioxide *(9q)*.



On standing at room temperature, or more rapidly on heating[16] to 40—70 °C, compound *(15)* eliminates CO_2 and isobutene to give *N*-fluorosulfonylacetoacetamide *(11)* in 85% yield.

Compound *(16)*, which is accessible from *N*,*N*-diethylacetoacetamide and FSI, also undergoes preferential closure of the oxathiazinone ring with alkali thus offering a preparative route to the amide *(9r)* in 54% yield (Table 5).

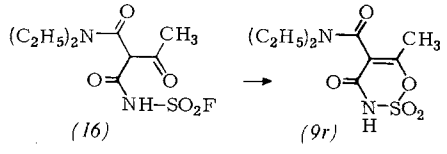


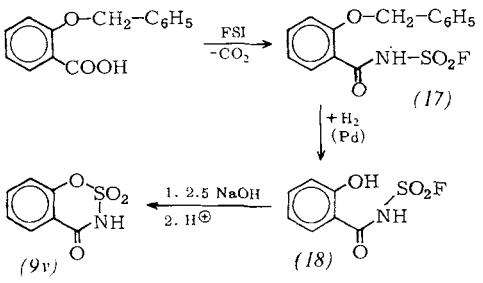
Table 5. Oxathiazinone dioxides from β-oxo acid derivatives.

Cpd.	R^1	R^2	Starting material	Yield [%]	M.p. [°C]
(9a)	H	CH_3	acetoacetic acid	55	123.5
(9p)	$COOC(CH_3)_3$	CH_3	*tert*-butyl acetoacetate	37	66
(9q)	COOH	CH_3	*(9p)*	90	104
(9r)	$CON(C_2H_5)_2$	CH_3	*N*,*N*-diethyl-acetoacetamide	54	162

2.5. The Benzyl Ether Method[17]

In spite of the versatility of the synthetic routes discussed so far, none can provide oxathiazinone dioxides having particular combinations of substituents in positions 5 and 6. Such compounds include the benzo derivative *(9v)*, which is interesting as a homolog of saccharin, and the unsubstituted parent compound *(9s)* (Table 6). The *N*-fluorosulfonylsalicylamide *(18)*, m.p. 156.5 °C, required for synthesis of the benzoxathiazinone *(9v)* cannot be obtained directly from salicylic acid and FSI since the reactivity of the phenolic hydroxyl group proves dominant[18][*]. However, *(18)* is readily prepared in 88% yield from *O*-benzylsalicylic acid[19] by reaction with FSI to give *(17)*, m.p. 115 °C, and subsequent hydrogenation in acetic acid solution to remove the benzyl group. If hydrogenolysis is conducted in the presence of sodium hydroxide solution then the desired benz-1,2,3-oxathiazin-4(3*H*)-one 2,2-dioxide *(9v)* is obtained (Table 6).

[*] Our own experiments with FSI led to *O*-(*N*-fluorosulfonylcarbamoyl)-salicylic acid having m.p. 111 °C.



If the protective group is hydrogenolyzed off in the alkaline medium then the amount of hydrogen taken up must be restricted to 1 mol since hydrogenolysis of the oxathiazinone ring will occur with more hydrogen.

The derivatives of *N*-fluorosulfonyl-β-hydroxyacrylamide *(20)* needed for preparation of 5-alkyloxathiazinone dioxides and the unsubstituted compound are produced by reaction of vinyl benzyl ethers with FSI in ether[20]. The reaction yields *N*-fluorosulfonyl-β-benzyloxyacrylamides *(19)* which suffer ring closure on catalytic hydrogenation in the presence of sodium hydroxide solution. The uptake of hydrogen must be limited to 1 mol here too (Table 6).

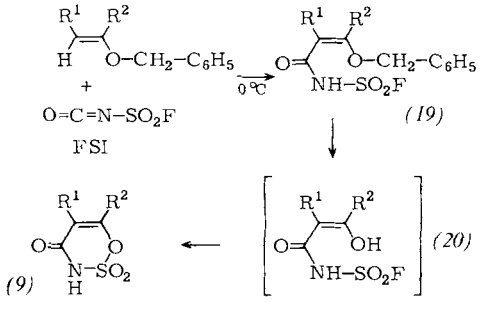


Table 6. Oxathiazinone dioxides prepared by the benzyl ether method.

Cpd.	R^1	R^2	*Starting material*	Yield [%]	M. p.	Sweetness
(9s)	H	H	benzyl vinyl ether [a]	39	107	+
(9t)	CH_3	H	benzyl propenyl ether [b]	22	81	+
(9u)	C_2H_5	H	benzyl butenyl ether [c]	25	73	+
(9v)	—(CH=CH)$_2$—		*O*-benzyl salicylic acid [19]	85	170	+

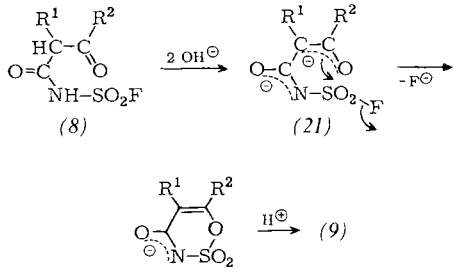
[a] Prepared by pressureless vinylation of benzyl alcohol at 130—150 C in the presence of potassium hydroxide. [b] Prepared by catalytic isomerization from allyl benzyl ether with potassium *tert*-butoxide in dimethyl sulfoxide at 25—40 C in 83% yield according to *C. C. Price* and *W. H. Snyder*, J. Amer. Chem. Soc. *83*, 1773 (1961). [c] Obtained from crotyl benzyl ether by catalytic isomerization with pentacarbonyliron and UV irradiation according to *P. W. Jolly*, *F. G. A. Stone*, and *K. Mackenzie*, J. Chem. Soc. *1965*, 6416.

2.6. *Ring Closure*

Cyclization of the intermediates prepared by the above methods is usually carried out in aqueous solution or suspension by slow addition of the necessary amount of caustic alkali, 2 mol being required for *N*-fluorosulfonyl β-oxo amides *(8)* and 3 mol for the tricarbonylmethane derivatives *(10)* accessible from β-dicarbonyl compounds if an acyl group has to be removed. As salts, the oxathiazinone dioxides are mostly readily soluble in water and are isolated from their solutions by acidification and extraction with organic solvents.

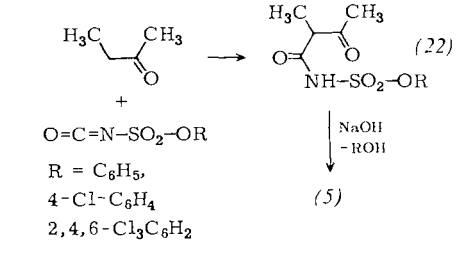
The ease of removal of the fluoride ion is surprising in view of the strength of the S—F bond. We assume that ring closure proceeds *via* nucleophilic attack by the ketonic oxygen on the fluorosulfonyl group in the dianion *(21)*.

An apparently obvious step would be to carry out the cyclization reactions with the analogous chlorosulfonyl derivatives from which the chloride ion is much more easily removed. Such attempts fail because the chlorosulfonyl group is rapidly hydrolyzed under the conditions used for the fluorides.

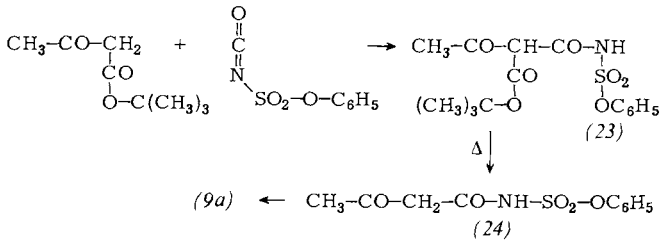


3. The Phenoxide Method[21]

A leaving group exhibiting sufficient resistance to hydrolysis and favoring cyclization is the phenoxide group. Ketones[15], β-diketones, and β-oxo carboxylic esters are attacked analogously by the aryloxysulfonyl isocyanates[22] and lead to *N*-aryloxysulfonyl β-oxo carboxamides, *e.g.* in the case of 2-butanone to the amides *(22)* and in that of *tert*-butyl acetoacetate to the tricarbonylmethane compound *(23)*, m.p. 92 C (dec.), 95% yield.



On warming, *(23)* readily loses CO_2 and isobutene to give *N*-phenoxysulfonylacetoacetamide *(24)*, m.p. 82 C, in 56% yield.

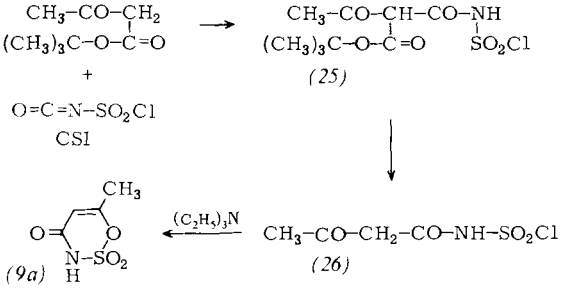


Treatment of *(22)* or *(24)* with caustic alkaline solutions removes the phenoxide ion to yield the oxathiazinone dioxides. The reaction conditions are strongly dependent upon the phenoxide group: whereas trichlorophenoxide departs easily like the fluoride ion, unsubstituted phenoxide requires considerably more stringent conditions.

4. The CSI Method[23]

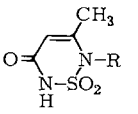
Removal of phenols or fluoride ions from the reaction products is difficult and, with regard to the use of oxathiazinone dioxides as sweeteners, gives rise to toxicological problems. It therefore appeared desirable to develop a synthesis starting from *N*-chlorosulfonyl β-oxo carboxamides. Such a route would also be attractive since all previous methods required fluorosulfonyl isocyanate which is difficultly accessible and exceptionally toxic.

Whereas ketones[15] do not react in just a single direction with chlorosulfonyl isocyanate (CSI), the more active β-dicarbonyl derivatives react very smoothly. For instance, *tert*-butyl acetoacetate in ether at 0—20 °C readily affords *tert*-butyl α-(*N*-chlorosulfonylcarbamoyl)acetoacetate *(25)*, m.p. 78 °C (dec.) in 91% yield[15]. On melting, this adduct liberates CO_2 and isobutene and furnishes *N*-chlorosulfonylacetoacetamide *(26)*, m.p. 86 °C, in 85% yield.



Unlike the fluoro- or phenoxy compound, *N*-chlorosulfonylacetoacetamide *(26)* rapidly reacts with water or alcohol at room temperature to give the sulfonic acid or its esters. In aprotic solvents such as ethyl acetate the oxathiazinone ring is readily closed with elimination of HCl on treatment with bases such as tertiary amines. This reaction is fast and gives good yields at −78 to 0 °C, possibly providing some indication of the intermediacy of the sulfonylamine (azasulfene)[24].

This cyclization is also possible with other amines. However, primary amines and ammonia also lead in part to formation of thiadiazinone dioxides *(27)*.



(27a), R = H [25], m.p. 174 C, yield 10%
(27b), R = CH_3, m.p. 162 C, yield 7%

Since the oxathiazinone dioxides are formed in a basic medium they are obtained as salts owing to the acidic nature of the —CO—NH—SO_2 group. Isolation of the acids is best performed by acidifying the aqueous salt solutions with mineral acids and extracting the oxathiazinone with ethyl acetate.

5. Properties and Reactions of Oxathiazinone Dioxides

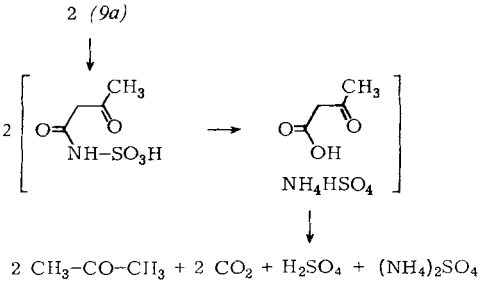
The oxathiazinone dioxides accessible by one of the above procedures are thermally and chemically stable crystalline substances that dissolve in the common organic solvents and, when only slightly substituted, also in water. As strong monobasic acids they are practically completely dissociated in water and form stable neutral salts having melting points above 200 °C with alkali metals and calcium (Table 7).

Table 7. Melting points and solubilities of some salts of 6-methyloxathiazinone dioxide *(9a)* in water.

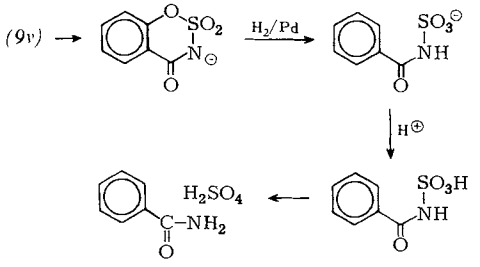
Cation		Na^+	K^+	Ca^{2+}	$[(C_2H_5)_3NH]^+$
M.p. [°C]		220	250	>310	68
Solubility [g/100 ml H_2O]	23 °C	340	25	120–130	830
	105 °C	580	135	180–190	∞

The steep temperature gradient of the solubility of the potassium salt in water makes it particularly suitable for purification of 6-methyloxathiazinone dioxide *(9a)*. 5,6-Dimethyl-*(5)* and the two ethylmethyloxathiazinone dioxides *(9b)* and *(9c)* exhibit such a high thermal stability that they can be distilled in a good vacuum or subjected to gas chromatography. The intense UV absorption at 228 nm ($\log \varepsilon \approx 4.0$) can be used to advantage for concentration determination.

The calcium salt of 6-methyloxathiazinone dioxide survives eight hours' heating at 120±2 °C of a 0.2% aqueous solution at pH 7 without measurable decomposition. The free 6-methyloxathiazinone dioxide *(9a)* decomposes when an aqueous solution is boiled to give 90% acetone alongside CO_2, ammonium sulfate, and sulfuric acid. These fragments suggest that cleavage proceeds *via* acetoacetic acid.

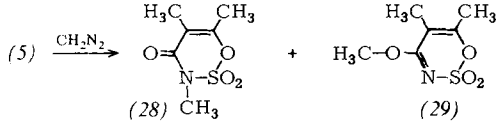


As already mentioned in Section 2.6, benzoxathiazinone dioxide *(9v)* undergoes ring cleavage in alkaline media on attack by catalytically activated (palladium) hydrogen (1 mol). The *N*-sulfonic acid can be precipitated in crystalline form and fragmented to benzamide and sulfuric acid by brief boiling in acid solution.

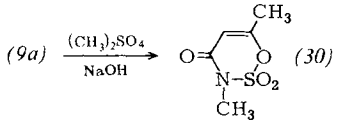


5,6-Dimethyl- and 6-methyloxathiazinone dioxide undergo a corresponding reaction with 2 mol of hydrogen. However, the *N*-sulfonic acids could not be detected in these cases: after hydrolytic release of the SO_3H group[126], ^1H-NMR spectra revealed mixtures of the amides with the free carboxylic acids.

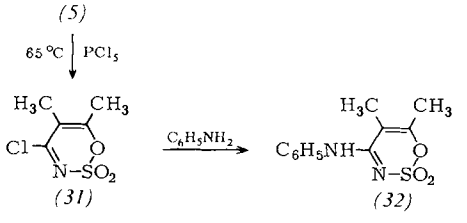
The strongly acidic proton of the oxathiazinone dioxides can be smoothly methylated by ethereal diazomethane, the product mixture containing *N*-methyl compounds with minor amounts of the *O*-methyl representative, as in the case of 5,6-dimethyloxathiazinone dioxide *(5)* [*(28)*, b.p. 66 C/0.01 torr, 68% yield; *(29)*, b.p. 110 °C/0.01 torr, m.p. 63 C, 16% yield].



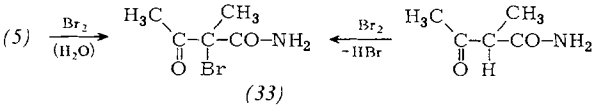
Methylation can also be accomplished by the action of dimethyl sulfate on the alkali metal salts of oxathiazinone dioxide, *e.g.* with the 6-methyl derivative *(9a)*. Reaction furnishes *(30)*, b.p. 85 °C/1 torr, m.p. 40 °C, in 40% yield.



A chlorine atom can be introduced at C-4 by phosphorus pentachloride in carbon tetrachloride solution. The resulting oxathiazine dioxide *(31)*, b.p. 98 °C/10^{-3} torr, 80% yield, is capable of further exchange reactions. For example, aniline gives the derivative *(32)*, m.p. 221 °C, in 48% yield.



In aqueous solution, bromine cleaves the oxathiazine ring of the dimethyl compound *(5)* to form α-bromo-α-methylacetoacetamide *(33)*, m.p. 68 °C, 53% yield. The same compound also results on bromination of α-methylacetoacetamide.



(33)

6. Relative Sweetness and Structure of Oxathiazinone Dioxides

Unsubstituted oxathiazinone dioxide *(9s)* and a number of slightly substituted derivatives exhibit varying degrees of sweetness. Since they also have an acidity comparable with that of mineral acids, taste comparisons are feasible only with the neutral alkali or alkaline earth metal salts. Table 8 lists those of the derivatives we have prepared which have a sweet taste, together with their relative sweetnesses. The parent compound proves to be the least sweet, and the 5-ethyl-6-methyl derivative the most sweet. Exchange of the two alkyl groups or shortening of the ethyl chain lowers the sweetness to half its original value.

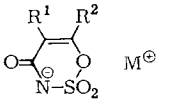


Table 8. Relative sweetness and LD_{50} of salts of oxathiazinone dioxides.

R^1	R^2	M	Relative sweetness [a]	LD_{50} [g/kg rat]
H	H	Na	10	
H	CH_3	Na	130	10.4
H	CH_3	K	130	7.4
H	CH_3	Ca	130	6.5
CH_3	H	Na	20	
CH_3	CH_3	Na	130	8.7
H	C_2H_5	Na	150	
C_2H_5	H	Na	20	
CH_3	C_2H_5	Na	130	
C_2H_5	CH_3	Na	250	9.9
H	n-C_4H_9	Na	30	
n-C_3H_7	CH_3	Na	30	
i-C_3H_7	CH_3	Na	50	
CH=CH—CH=CH		Na	*ca.* 50	
C_2H_5	n-C_3H_7	Na	70	

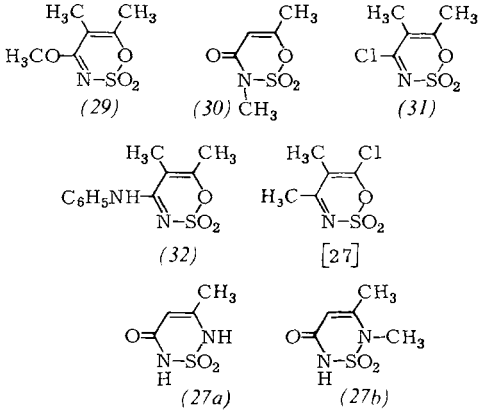
[a] Relative to cane sugar in 4% aqueous solution.

Our attention has become focused mainly on the 6-methyl derivative *(9a)* whose potassium or calcium salt is about four times sweeter than cyclamate and stands out from the others in the purity of its sweet taste. Tests with various preparations and juices show the taste of these salts to fit in particularly well for use as a sweetening agent. Their high solubility in water (see Table 7) also offers advantages in use since most synthetic sweeteners display an unsatisfactory solubility.

The salts of *(9a)* also prove sufficiently stable to hydrolysis for practical purposes. Even in highly acidic beverages

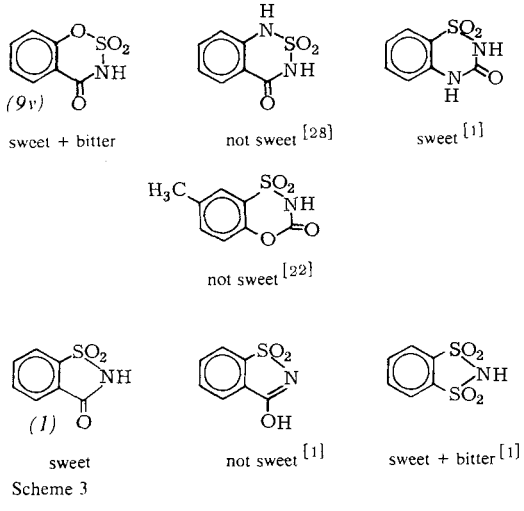
they remain unchanged for months and no deterioration in their purity of taste can be registered.

The acute toxicity was determined in various cases and is likewise given in Table 8. The substances tested can thus be regarded as practically nontoxic. Meanwhile, a 95-day feeding test on rats has been carried out with the calcium salt of the 6-methyl compound *(9a)*, with up to 5% of *(9a)* in the feed. No evidence was found that ingestion of compound *(9a)* had an influence on the increase in body weight, food consumption, blood count, serum enzyme values, urinalysis, the findings of macroscopic post mortem examinations, and organ weights. No deviations from control animals could be detected during animal growth or on histological examination of their organs. As already mentioned, these animal experiments represent only partial results and any toxicological assessment of the salts of *(9a)* with regard to their suitability as sweeteners will have to await their completion.



Scheme 2

The question of their metabolism will also have to be elucidated. If a hydrolytic route is followed, *i. e.* metabolism commences with ring cleavage to give acetoacetamide-*N*-sulfonic acid, further degradation should yield physiological substances. This is yet another reason why we prefer



Scheme 3

the salts of 6-methyloxathiazinone dioxides; they are derivatives of acetoacetic acid.

As found with other sweeteners[1, 7], any functional change of the system leads to complete loss of the sweet taste. Scheme 2 shows some derivatives completely devoid of any sweet taste.

Scheme 3 shows a number of benzo heterocyclic compounds some of which are sweet while others have no sweet taste. It accordingly still appears difficult to predict the property of sweetness for a given compound.

Application of Hansch analysis[29] to the problems of sweetening action may possibly provide a further insight into the underlying principles.

We are grateful to Dr. H. Bestian for his active interest and numerous valuable discussions.

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Methylchlorophosphanes and Their Reaction Products

By Horst Staendeke and Hanss-Jerg Kleiner[*]

Dedicated to Professor Werner Schultheis on the occasion of his 70th birthday

Methyldichlorophosphane and dimethylchlorophosphane can be prepared only with considerable difficulty. The ease with which they yield numerous reaction products is an indication of the pronounced reactivity of these organohalophosphanes. Possible applications of such organophosphorus compounds exist *inter alia* in the fields of plant protection, corrosion prevention, and flame retardants, as well as in the catalysis of gas phase reactions, for instance the desulfurization of gas mixtures.

1. Introduction

The large number of publications in the area of organophosphorus chemistry provides a measure for the interest commanded by this class of compounds. This applies both to the synthesis of new compounds and to the introduction of phosphorus-containing functionalities into other molecules in order to modify their chemical or physical properties.

As an example, the hydrolysis-resistant linkage of the dimethylphosphane oxide group, $(CH_3)_2P(O)$—, to organic compounds gives rise to a variety of widely differing effects, such as improved solubility, enhanced surface activity, and antistatic action.

The reduction in flammability of combustible compounds that can be achieved by incorporation of such groups has recently become of particular significance. Owing to the high phosphorus content in the small molecular group, an adequate retarding effect is provided by incorporation of relatively small amounts of the phosphorus component. So slight are the resultant changes in the skeleton of polymeric compounds that their other physical and technological properties are largely retained.

Because of their relatively poor accessibility and their special properties the present article will concentrate on the methyl compounds. (Surveys of organophosphorus compounds will be found in refs.[1, 2].)

The methylchlorophosphanes are colorless liquids that can be distilled without decomposition (CH_3PCl_2: b. p. 82 °C[3], m. p. −80 °C[17], $d_{20} = 1.30$[3], $n_D^{20} = 1.4940$[3]; $(CH_3)_2PCl$: b. p. 79 °C[3], m. p. −2 °C[17], $d_{20} = 1.07$[3], $n_D^{20} = 1.4760$[3]) and are readily soluble in inert organic solvents; their pronounced sensitivity to moisture and air [$(CH_3)_2PCl$ undergoes spontaneous combustion on admission of air] requires special apparatus for all operations.

2. Synthesis of Methyldichlorophosphane[1]

Preparations starting from methanephosphonous acid, $CH_3P(O)(H)OH$, and derivatives, from methylphosphane, from tetramethylcyclotetraphosphane, and from organometallic compounds are of little interest because the starting materials themselves are not readily available.

2.1. Synthesis from Methyltrichlorophosphonium Tetrachloroaluminate[1]

In contrast, methyldichlorophosphane is readily obtained by reduction (*e.g.* with aluminum) of the complex *(1)* formed in the Kinnear-Perren reaction

$$PCl_3 + AlCl_3 + CH_3Cl \rightarrow [CH_3PCl_3]^{\oplus}[AlCl_4]^{\ominus}$$
(1)

and subsequent addition of an equimolar quantity of alkali metal chloride.

Partial hydrolysis of the complex *(1)* or reaction with sulfur yields phosphonic dichloride, $CH_3P(O)Cl_2$, or thiophosphonic dichloride, $CH_3P(S)Cl_2$, as intermediate which may be converted into methyldichlorophosphane on treatment with reducing agents (yields *ca.* 50%) or desulfurating agents (yields up to 92%) respectively.

2.2. Synthesis by Gas Phase Reactions

2.2.1. Reaction of Phosphorus Halides with Methane[1]

The reaction of phosphorus(III) chloride and methane at around 600 °C leads to about 20% conversion into methyldichlorophosphane with residence times as low as 0.3 s. Apart from oxygen and chlorine, suitable catalysts include carbon tetrahalides[4] and phosgene[5].

Methyldichlorophosphane was produced for several years by this method in the USA.

2.2.2. Reaction of Red Phosphorus with Methyl Halides[1]

Above 200 °C red phosphorus reacts with methyl chloride to give methylchlorophosphanes. Optimum conditions for the copper-catalyzed reaction exist when the catalyst mass consists of red phosphorus and copper powder and the temperature is kept at 350—360 °C. The major product is methyldichlorophosphane; the yield (based on reacted methyl chloride) is around 25%.

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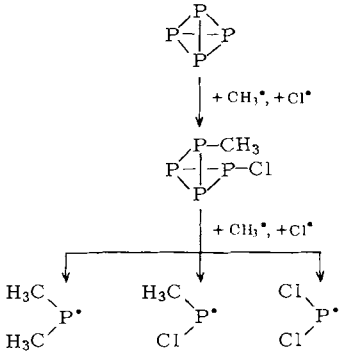
The high price of red phosphorus and the complicated preparation of the catalyst/phosphorus mixture would oppose attempts to run this reaction on an industrial scale.

If a mixture of phosphorus vapor and methyl chloride is passed over activated charcoal[6,7] at 350 °C, the main reaction products are methyldichlorophosphane and dimethylchlorophosphane. The yield amounts to 70% (again based on reacted methyl chloride).

2.2.3. Reaction Course

The gas phase alkylation reactions probably proceed *via* a radical mechanism[8] whose first step is assumed to consist in homolysis of the alkyl halide (Scheme 1). In accord with this assumption, the complete range of conceivable phosphorus compounds—$(CH_3)_3P$, $(CH_3)_2PCl$, CH_3PCl_2, and PCl_3—could be detected. Further evidence for a radical mechanism comes from the appearance of numerous by-products containing no phosphorus which could be formed by recombination reactions (Scheme 2).



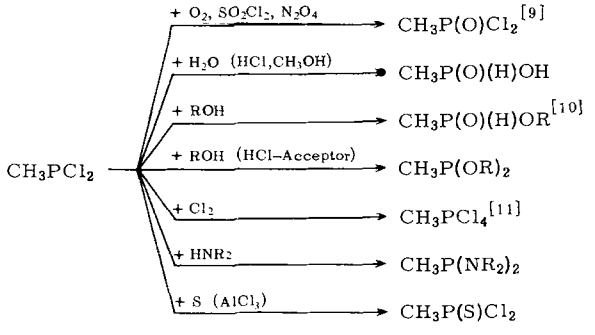
Scheme 1. Gas phase reaction of red phosphorus with methyl chloride.

$$CH_3^{\bullet} + CH_3Cl \rightarrow CH_4 + CH_2Cl^{\bullet}$$
$$2\ CH_3^{\bullet} \rightarrow C_2H_6$$
$$CH_3^{\bullet} \rightarrow CH_2{:} + H^{\bullet}$$
$$2\ CH_2{:} \rightarrow C_2H_4$$
$$2\ H^{\bullet} \rightarrow H_2$$

Scheme 2. By-products devoid of phosphorus formed in the gas phase reaction of red phosphorus with methyl chloride.

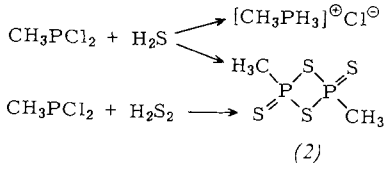
3. Reactions of Methyldichlorophosphane

Owing to the pronounced reactivity of methyldichlorophosphane, many of its products are accessible by simple reactions (Scheme 3).



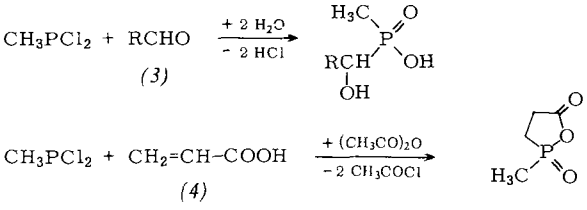
Scheme 3. Reactions of methyldichlorophosphane.

In the reaction with sulfur-hydrogen compounds, hydrogen sulfide[12] also acts as a reducing agent whereas with disulfane[13] the only reaction occurring is sulfuration to give *(2)*.

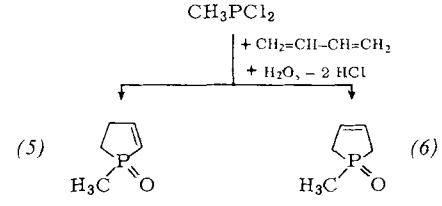


(2)

A new phosphorus-carbon bond can result from a large number of reactions[14]. Particular importance attaches to reactions with compounds of type *(3)* and *(4)* bearing C=O and C=C functions respectively.



A route to tertiary cyclic phosphane oxides such as *(5)* and *(6)* is provided by condensation reactions with dienes[15] (Diels-Alder reaction).



4. Synthesis of Dimethylchlorophosphane[1]

The preparation of compounds with the $(CH_3)_2P$ group proves considerably more difficult than that of CH_3P derivatives. Processes such as the reaction of dimethylphosphinous amides, $(CH_3)_2PNR_2$, with hydrogen chloride or of dimethylphosphane or tetramethyldiphosphane with chlorine therefore remain of no significance.

4.1. Synthesis from Dimethyldichlorophosphonium Tetrachloroaluminate[1]

If methyldichlorophosphane is available as starting compound, it can be subjected to a Kinnear-Perren type reaction:

$$CH_3PCl_2 + AlCl_3 + CH_3Cl \rightarrow [(CH_3)_2PCl_2]^{\oplus}[AlCl_4]^{\ominus}$$

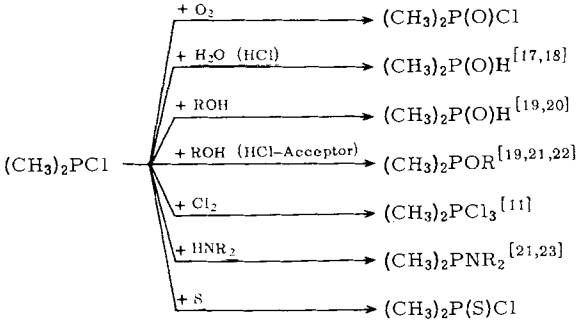
Reductive work-up of the complex yields dimethylchlorophosphane. As in the case of the monomethyl compound, this complex also furnishes the thiophosphinic chloride $(CH_3)_2P(S)Cl$, whose desulfuration (preferably with trialkylphosphanes) affords good yields of dimethylchlorophosphane.

4.2. Synthesis by Gas Phase Reactions

The low thermal stability of the dimethyl compound precludes its preparation by both the high-temperature reaction of phosphorus(III) chloride with methane and the copper-catalyzed reaction of red phosphorus with methyl chloride. However, the reaction of phosphorus vapor with methyl chloride in an active charcoal zone[6] at 350 °C yields a mixture of methylchlorophosphanes containing at least 30 % of dimethylchlorophosphane[7]. The two components can be isolated by phase separation[16] since, after conversion into the hydrogen chloride adduct, dimethylchlorophosphane is no longer miscible with methyldichlorophosphane.

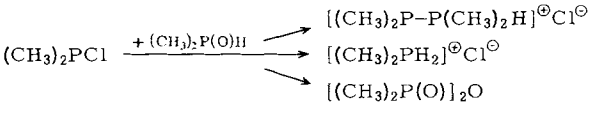
5. Reactions of Dimethylchlorophosphane

Dimethylchlorophosphane also readily undergoes a variety of reactions (Scheme 4).



Scheme 4. Reactions of dimethylchlorophosphane.

The reaction of dimethylchlorophosphane with its hydrolysis product dimethylphosphane oxide[24] appears highly complicated (Scheme 5).

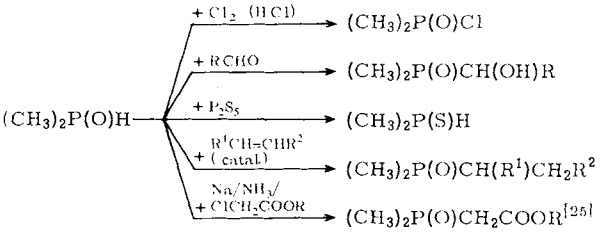


Scheme 5. Reactions of dimethylchlorophosphane with dimethylphosphane oxide.

The transition from dimethylchlorophosphane to the tertiary phosphanes and phosphane oxides can be accomplished in a variety of ways, *e. g.* by reaction with unsaturated compounds or carbonyl compounds in which a new P—C bond is formed.

5.1. Reactions of Dimethylphosphane Oxides

A number of reaction products of dimethylchlorophosphane can be advantageously prepared from dimethylphosphane oxide[21]; the latter compound is stable to air and only moderately hygroscopic (m.p. 39—41 °C; b.p. 54 °C/1 torr) (Scheme 6).

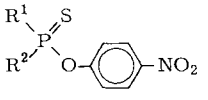


Scheme 6. Reactions of dimethylphosphane oxide.

6. Applications

6.1. Plant Protection

Numerous biologically active derivatives of phosphonic and phosphinic acids have been synthesized in connection with the development of biocidal phosphoric esters. The difficulties encountered in the preparation of the starting materials, however, make such products expensive and thus oppose their widespread use. In addition, a general observation regarding toxicity to warm-blooded animals and insecticidal activity must be taken into account, which will be illustrated here for the transition from phosphoric esters such as methylparathion *(7)* to the corresponding phosphonic *(8)* and phosphinic acid derivatives *(9)* (Table 1)[26].



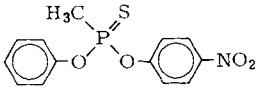
(7) – *(9)*

Table 1. Toxicity (rat) and insecticidal activity (aphid) of methylparathion *(7)* and the corresponding phosphonic *(8)* and phosphinic acid derivatives *(9)*.

Cpd.	R^1	R^2	Toxicity LD_{50} [mg/kg]	Insecticidal activity Conc. [%]	Mortality [%]
(7)	CH_3O	CH_3O	20	0.0001	100
(8)	CH_3O	CH_3	1	0.001	100
(9)	CH_3	CH_3	100	0.1	100

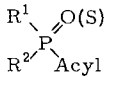
Oxidative and hydrolytic degradation of phosphonic and phosphinic esters, like that of the phosphoric acid derivatives, leads to harmless compounds, the acids.

The only insecticide we know to possess a methyl-phosphorus functionality, Colep® *(10)*[27], is remarkable because



(10)

it does not fit into the formula scheme *(11)* of the Schrader rule[26] for biologically active phosphorus compounds. In Colep an alkoxyl group is replaced by phenoxyl.



(11), R^1, R^2 = Alkyl, Alkoxy, Amino

6.2. Dyeing

On dyeing of synthetic fibers or mixed textiles in aqueous dye baths, addition of organophosphorus compounds[28], *e. g.* dimethyl methanephosphonate, improves the uniformity and depth of dyeing.

The use of carriers which "open up" the fiber and thus promote better penetration of the dye can impair the light-fastness of the dye if residues of certain carrier types remain in the fiber. However, addition of phosphane oxides[29], *e.g.* octyldimethylphosphane oxide, to the dye bath, the after-treatment bath, or the carrier preparation almost completely eliminates loss of light-fastness.

When the purification of the waste water from aqueous dye liquors proves particularly difficult an obvious solution is to carry out the process in organic solvents (in the presence of small amounts of water). Work-up of the spent dye liquor reduces to distillation of the water/solvent mixture. However, numerous commercial dyes are insufficiently soluble in organic solvents. A considerable improvement results on use of organophosphorus compounds[30], *e.g.* decyldimethylphosphane oxide:

1) the ambivalent character of the phosphane oxide (hydrophilic methyl group, lyophilic decyl group) effects ready emulsifiability of the water in the solvent;

2) the pronounced solubilization property considerably increases the dye concentration in the organic dye liquor and thereby permits uniform and deep dyeing with a much broader range of dyestuffs.

6.3. Corrosion Prevention

An important requirement for lasting protection against corrosion lies in adequate adhesion of the coating to the metal surface. Treatment of the metal with a compound with which it reacts and yet which possesses sufficient "affinity" for the protective coating should consequently have a particularly favorable effect.

The compound dimethyl-2-oxopropylphosphane oxide, $(CH_3)_2P(O)CH_2COCH_3$, represents a suitable chemisorption agent for treatment of steel, aluminum, copper, and titanium surfaces[31]. A chemisorption layer is presumably formed with the surface oxide coating, with participation of the C=O and P=O groups, whose predominantly lyophilic character ensures good binding with the protective paint.

6.4. Catalysis

The reaction

$$2H_2S + SO_2 \rightarrow 3S + 2H_2O$$

represents a possible method for removal of sulfur compounds from gaseous mixtures. If the reaction is carried out in polar aprotic solvents in the presence of phosphane oxides[32], *e.g.* trimethylphosphane oxide, the sulfur content can be lowered almost to the detection limit and crystalline sulfur obtained simultaneously in a purity exceeding 99.8%. This gas purification reaction has a broad scope: the content of hydrogen sulfide can vary between 0.0001 vol-% and more than 5 vol-%.

6.5. Formulation of Detergents

The development of new detergents must take account of the following properties: stability towards water-hardeners, powerful washing action, high dissolving power for calcium soaps, biodegradability, and resistance to hydrolysis. A group of trialkylphosphane oxides[33] in which one alkyl group contains 10—18 C atoms and the other two not more than 3 C atoms fulfills these and further stipulations:

thermal stability (important for spray drying of granular detergents)

low hygroscopicity (to avoid caking of granular detergents)

bacteriostatic activity (important for use as cold detergents).

These favorable properties suggest applications in detergents, soaps, liquid cleansers, and scouring agents[33].

6.6. Flameproofing[34, 35]

Increasing attention has recently been paid to the reduction of flammability of flammable materials for a number of applications (*e.g.* internal fittings in aircraft and automobiles, building units, textiles for hospitals). Corresponding legislation has already been introduced, particularly in the USA. These stipulations are being met by manufacturers in the development of flame resistant products. The varying combustion characteristics of plastics and textiles require development of specific flameproofing agents.

The elements chlorine, bromine, nitrogen, phosphorus, and antimony in the form of suitable compounds, which are present as additives or chemically bound to the materials concerned, have proved to be effective for this purpose. Numerous concepts exist concerning the mode of action of the flameproofing agents but we shall not go into details here. Experience has shown phosphorus to be the most effective agent. Between 1 and 6% of phosphorus must be incorporated, depending upon the chemical formulation of the material, to provide a flame-resistant product; *e.g.* cellulose becomes self-extinguishing at a 2.5—4% P content, and nonflammable at 7—8%. It was observed that the effectiveness as flameproofing agent (based on the phosphorus content) decreases along the series phosphane oxide > phosphinic acid > phosphonic acid > phosphoric acid.

An additional advantage of using phosphane oxides and derivatives of phosphinic and phosphonic acids, apart from the resistance to hydrolysis, lies in the fact that the molecular group introduced becomes firmly bound to the polymer and its chemical structure can be modified. This permits "reactive" incorporation into the matrix of polymers which has only a slight influence on the other physical and technological properties of the host material even after prolonged usage. The flameproofing treatment of cellulosic fibers will be mentioned as an example.

Ignition of cotton is preceded by depolymerization (above 180 °C) and pyrolysis to give combustible cleavage products whose concentration at 350 °C becomes so great that a flammable mixture is present. The mechanism of the pyrolytic processes is modified by the flameproofing agents in that they

1) lower the pyrolysis temperature,

2) increase the amounts of non-combustible gaseous cleav-

age products (CO_2, H_2O) because they exhibit, *inter alia*, a dehydrating action[*],

3) increase the pyrolysis residue from 10 to about 50% so that only 30—40% of flammable products are formed instead of 80%.

Dimethylphosphinic chloride[36] or methanephosphonic anhydride[37] have been proposed as flameproofing agents that are linked to the hydroxyl groups of cellulose. Greater importance attaches to the processes in which an initial impregnation of the textile with the flameproofing agent is followed by a condensation reaction with a second component with the aim of fixing the substrate to the fiber[34, 38].

The flameproofing agents THPC $[(HOCH_2)_4P^+Cl^-]$ and Pyrovatex® $[(CH_3O)_2P(O)CH_2CH_2CONHCH_2OH]$ used in this process are of particular significance. The flameproofing achieved by this process is washproof and hardly impairs the properties of the fiber (feel, tear strength, wear resistance, crease recovery).

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[*] Fireproofing agents based on phosphorus evolve phosphoric acid during a fire. As a dehydrating agent this compound favors the degradation of organic products to carbon.

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Possibilities and Limitations of Delegated Literature Searches by Computer

By Robert Fugmann and Gottfried Ploss[*]

Dedicated to Professor Werner Schultheis on the occasion of his 70th birthday

The present-day chemist is constantly on the lookout for information which may be useful to his work. If he is able to define his interests precisely enough then he can avail himself of information scientists and of specialized literature stores. However, retaining access to such information, which only he himself can subjectively judge for relevance to his work, and which most often constitutes a powerful incentive to his creative thinking, will always require his own "browsing" literature studies or personal contacts. These are the limitations of any delegated literature search.

As a result of the steadily growing flood of publications in the natural sciences, it is no longer possible for the individual scientist himself to keep a constant watch for new publications in his field. This is due simply to lack of time; moreover, he also lacks the special knowledge required to efficiently search through large mechanized files. He must therefore pass on his literature requirements to institutions whose function it is to satisfy the information needs of others. Institutions of this kind have sprung up throughout the world for a wide range of specialist fields as a result of the recognition that it is only through their aid that optimum use can be made of the vast quantity of information that exists. Two examples of institutions that carry out delegated literature searches of this nature on a large scale in the field of chemistry are the "IDC Internationale Dokumentationsgesellschaft für Chemie mbH" in Frankfurt/Main, which undertakes retrospective and current awareness searches in its files of (at present) some 1/2 million publications, and "Chemie Information und Dokumentation Berlin", a division of the Gesellschaft Deutscher Chemiker, which searches the latest additions to the "Chemical Abstracts Condensates" magnetic types.

These large stores offer the chemist new possibilities for keeping abreast of the latest developments if he uses them properly, *i.e.* if the limitations of any delegated search are borne in mind in the formulation of the search and in the evaluation of the results. What then are the limitations of delegated searches?

When the chemist himself searches the specialist literature for publications that are relevant to his work, he allows himself to be guided largely by intuition and by his personal interests at that particular time. He may start the search with an example of a type of reaction in which he is interested, and continuously modify the objective of the search according to the nature of the publications found, their number, *etc.* The most valuable results of literature searches carried out personally are often far removed from the formulation of the problem with which the search was started. The searcher feels himself under no obligation to define his problem at any stage in his literature search.

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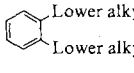
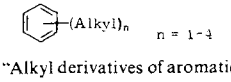
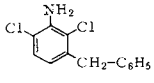
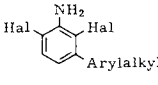
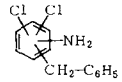
If he delegates his search, on the other hand, the continuous subjective reorientation of the search according to the publications found is no longer possible. He must now define his objective to the searcher by specifying in advance the characteristics that a publication must possess in order to be relevant to his work. In reply, therefore, he can expect to receive only publications that possess *at least the conceptual features that he himself stipulated in his phrasing of the inquiry*. This means, however, that in a delegated literature search he no longer receives suggestions from sources whose features differ from those specified, and which would have led so profitably to the continuous modification of his search objective.

If answers that did not possess all the features required in advance, *i.e.* that were *more general* than the formulation of the problem, were permitted in a delegated literature search, it would no longer be possible to avoid large numbers of references to very general publications or patent claims. An inquiry for "dimethylbenzenes", for example, would then also include "alkylaromatic hydrocarbons" or "hydrocarbons" as answers.

To illustrate this situation, which is unfamiliar to the chemist, Table 1 shows which general answers (right-hand column) are not to be expected to a specific inquiry of the type shown in the left-hand column.

The structures shown in the right-hand column cannot be retrieved because they do not satisfy all the requirements

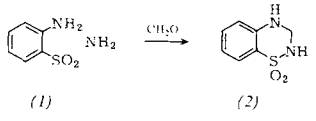
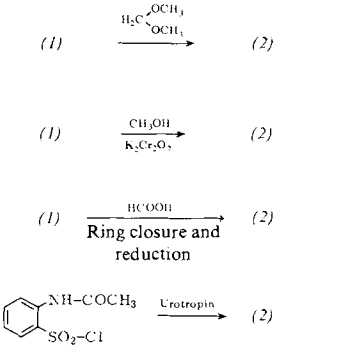
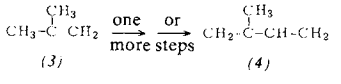
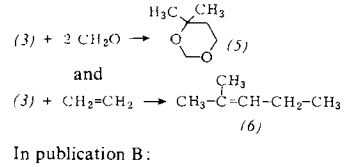
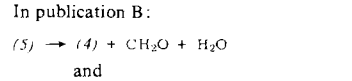
Table 1. Problems of search objective definition for substances.

Inquiry	Answers that cannot be retrieved with this inquiry
	  "Alkyl derivatives of aromatic hydrocarbons"
	 

of the inquiry. If structures of these types are also desired as answers, therefore, the search must be given a more general formulation. For example, the relative positions of the substituents must not be specified, or the alkyl substituent must not be restricted to methyl. Such a generalized inquiry will also lead to retrieval of all the more specific structures.

If certain starting materials are called for in addition to the desired reaction product, this must also number among the conceptual requirements of a search. Publications in which no starting materials or different starting materials are mentioned will not then be retrieved as answers. Even if the publication mentions starting materials from which the starting material required in the search might readily have been formed as an intermediate during the reaction, the publication is not retrieved. The same is true of any intermediates that are specified in the search. Here again, no answer is obtained if the author has not indicated an intermediate or has postulated an intermediate different from that required in the search formulation.

Table 2. The problem of search objective definition for reactions.

Inquiry	Answers that cannot be retrieved with this inquiry
 (1) (2)	 (1) → (2); (1) → (2); (1) → Ring closure and reduction → (2); → (2)
 (3) (4)	In publication A:  (3) + 2 CH_2O → (5); and (3) + $CH_2{=}CH_2$ →  (6); In publication B: (5) → (4) + CH_2O + H_2O; and (6) → (4) + CH_4

If in a mechanized literature search a certain starting material and a particular reaction product are required (no matter how many reaction steps are involved) then obviously only such documents can be expected as responses in which both compounds had actually been described. This requirement is met neither in the case of the publication A nor in that of B in Table 2. However, if one searches the store with two separate inquiries, for the starting material and for the desired reaction product respectively, then the publications A and B will be retrieved with certainty. Human reasoning can then easily recognize the relation between both publications in the sense of the original inquiry.

Particular caution in phrasing the inquiry is necessary if an abstract has been used instead of the original publication in the compilation of the store. To save space, the abstractor must often incorporate the details of the original into the abstract in a generalized form; instead of "ethyl or propyl or butyl", for example, he may simply use "alkyl". It is merely for these reasons that an inquiry may have to be formulated in a suitably generalized form.

All the above examples show that in a delegated machine search, if important suggestions from sources whose peculiarity cannot be foreseen are not to be completely missed, a more general formulation of the search is always necessary than in cases where the search is being carried out by the inquirer himself. If these precautions are observed, the danger of loss of information is largely eliminated.

However, the generalization of a search may lead to the other disadvantage that the searcher is occasionally also provided with references that he regards as "ballast" from the standpoint of his present subjective interest. Perhaps he is already sufficiently familiar with these publications, or the yield and purity of the products described in them are unsatisfactory, *etc.* Since the inquirer can never exhaustively define his interests, however, he cannot expect them to be taken fully into account by another person to whom the literature search has been delegated. The only way in which all such "ballast" could be definitely avoided would be to avoid any generalization, and this would necessarily result in a serious loss of relevant information, as was shown above.

The recommendation that a search should be reasonably generalized is thus merely intended to avoid the danger of loss of unforseeably valuable information in the delegated literature search. If this danger does not arise in a given instance, or if it is consciously accepted by the inquirer, there is no obstacle to a highly specific inquiry in high-performance documentation systems.

In phrasing the inquiry, the inquirer must decide what degree of generalization is permissible for him without including too much and too irrelevant material. This will depend on whether the search is intended to be used as a check on the patent situation, as a search for novelty, or for synthetic work. On the other hand, only the information scientist knows the depth of detail with which the literature has been analyzed, and what details in an inquiry would therefore constitute unsatisfiable search conditions. Since considerable cost is involved in the deep analysis of specialist literature for machine searches and in continuously keeping this literature available for searches in a store, only the specialist literature for a limited selection of fields can always be included. Even here however, to reduce costs, pure textbook knowledge such as is often provided in publications alongside new knowledge (preparation of starting materials, degradation reactions for structural elucidation, *etc.*) cannot normally be included. In the case of patents, the description of the state of the art must usually be excluded. Information of this nature cannot therefore be expected from the store.

It must also be made clear whether a given formulation of an inquiry is intended simply as an example of a much

wider problem or whether it is intended as the problem itself. If we have to deal with only one example, more or less arbitrarily selected from a multitude of equivalent ones, then the inquiry must be generalized appropriately. However, the information scientist occasionally has to recommend greater specificity in the formulation of a search. For, on the basis of the composition and size of the store, he can often forsee that a given formulation would produce too many answers. An excessively comprehensive search result indirectly leads once more to loss of information, since it can be followed up only in part by the inquirer, who will then content himself with, say publications that appeared during the last year or in certain journals or patent classes.

The cooperation of the scientist with an institution to which he can delegate searches always calls for a certain refinement of his thinking in literature searches. His phrasing of an inquiry often forces him to realize how subjective and ill-defined many of his literature problems are, a realization that is not really surprising when one considers what a large part intuition and imagination play in research work. On the one hand, he is presented with new and promising search possibilities through the perfected search techniques of such institutions, which are run by information specialists. On the other hand, he cannot expect such institutions to solve all his information problems. Many stimuli for his work arise simply from his immersion in the specialist literature, and apart from contact with other workers, this is the only way for him to keep abreast of fundamental innovations in science in general and in his field in particular. Even in an age of very large stores that can be searched with a high degree of efficiency, therefore, there will still be a place for the continuous publication of specialist literature and the scientist's own literature studies.

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Chemical Applications of Raman Spectroscopy[**]

By Bernhard Schrader[*]

Raman spectroscopy is—like infrared spectroscopy—a method for the study of the vibrations of molecules and crystals. The two methods are complementary: if a vibration results in a change of the polarizability of a molecule, it is Raman active; if a change in the molecular dipole moment results, it is infrared active. Vibrations of nonpolar groups and totally symmetrical vibrations of molecules are often only Raman active. IR and Raman spectra together give information about the symmetries and structures of molecules and crystals and about the properties of chemical bonds and intermolecular interactions. Until about 10 years ago Raman spectra could only be recorded on relatively large amounts of essentially colorless substances. After the advent of laser light sources the situation changed completely. The amount of sample substance required is now in the region of milli- and micrograms. Gases, liquids and solid samples, especially air-sensitive and reactive substances, single crystals, crystal needles and filaments as well as aqueous solutions can be readily investigated. The identification of molecules and the elucidation of molecular structures, biochemical analysis, and control of environmental pollution are important applications of Raman spectroscopy. Raman spectroscopy now constitutes an additional powerful tool in instrumental analysis.

1. Introduction

Raman spectroscopy, which until recently had been used relatively infrequently, now attracts the interest of many chemists and physicists. Modern Raman spectrometers fitted with laser light sources have greatly facilitated the measurement of Raman spectra. The number of instruments in use and the number of relevant papers being published have increased considerably. Raman spectroscopy has found many new applications; many chemists presently using IR, UV, NMR, and mass spectroscopy are now considering whether they should resort to Raman spectroscopy and if purchase of a Raman spectrometer would justify itself. This paper is intended to help answer this question. The fundamentals of Raman spectroscopy, its applicability to chemical problems, and also its limitations will be considered.

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[**] See also: *B. Schrader* and *W. Meier*: Raman/IR Atlas. Verlag Chemie, Weinheim 1974. Here the reader will find a systematic collection of Raman and IR (FIR) spectra of *ca.* 1000 typical compounds (combinations of the most important molecular skeletons and substituents) including polymers and complex molecules of biological interest. This atlas will serve as a basis for automatic evaluation of spectra.

Comprehensive accounts of the fundamentals and applications can be found in the classic works of *Kohlrausch*[1], *Herzberg*[2,3], *Brandmüller* and *Moser*[4], *Wilson*, *Decius*, and *Cross*[5], *Colthup*, *Daly*, and *Wiberley*[6], and other authors[7-12]. The special problems of Raman spectroscopy with laser light sources are discussed in several monographs[13-17]. A number of reviews deal with other problems: sample preparation and measurement technique[18], chemical applications[19-21], properties of the instruments[22,23], theory[24], and applications to problems in physics[25-27]. Access to individual works is facilitated by bibliographies with "multidimensional indexes" or "SDI" documentation services[27a,27b].

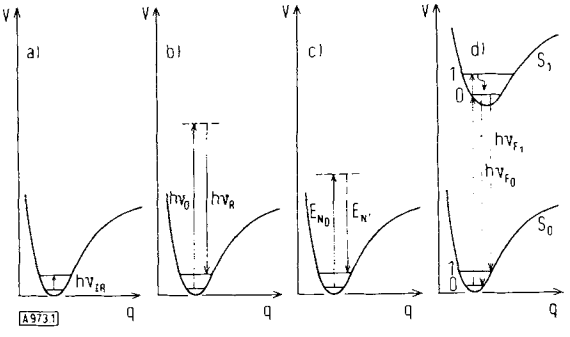


Fig. 1. Term diagrams of different methods for the observation of vibrational states: a) by IR spectroscopy ($h\nu_s = h\nu_{IR}$), b) by Raman spectroscopy ($h\nu_s = h\nu_0 - h\nu_R$), c) by neutron spectroscopy ($h\nu_s = E_{N_0} - E_{N'}$), d) by fluorescence spectroscopy ($h\nu_s = h\nu_{F_0} - h\nu_{F_1}$). S_0 = ground state, S_1 = excited state of the valence electrons. For details see text.

2. Fundamentals

2.1. The Methods of Vibrational Spectroscopy

Molecules consist of atoms, which are joined by elastic bonds. Such systems can perform vibrations. An n-atomic non-linear molecule may perform $3n$-6 independent normal vibrations whose frequencies ν are of the order of $10^{12} \ldots 10^{14}$ Hz, or given as wave numbers, $\tilde{\nu} = \nu/c$, about $10 \ldots 4000\,\mathrm{cm}^{-1}$. There are several ways in which these molecular vibrations can be observed. Figure 1 shows the potential energy V of a diatomic molecule as a function of the interatomic distance q together with the energy levels of a vibrational ground and excited state. Molecular vibrations can be excited directly by light quanta if their energy $h\nu$ is equal to the energy difference between the ground level and the excited vibrational level (Fig. 1a). Suitable light quanta belong to the infrared region of the electromagnetic spectrum ($\tilde{\nu} = 10 \ldots 4000\,\mathrm{cm}^{-1}$, $\lambda = 1000 \ldots 2.5\,\mu$). The energy $h\nu_{IR}$ corresponding to the absorption bands in the IR spectrum is equal to the energy $h\nu_s$ of the vibrational states of the molecule $h\nu_s = h\nu_{IR}$. On the other hand, molecular vibrations can be observed indirectly: by the Raman effect. When molecules are illuminated by a strong incident beam of monochromatic light some light quanta are scattered inelastically by the molecules. A part of the energy of the quanta $h\nu_0$ is transferred to the molecules, in the course of which vibrations are excited (Fig. 1b). The energy $h\nu_R$ of the inelastically scattered light quanta can be analyzed by means of a spectrometer. From the resulting Raman spectrum the vibrational energy of the molecules is given by $h\nu_s = h\nu_0 - h\nu_R$. Other possible methods for the study of vibrations in molecules are: analysis of the inelastic scattering of monoenergetic neutrons of energy E_{N_0} (Fig. 1c)[28] and of the fluorescence spectrum (Fig. 1d)[29,30]. However, these methods are by no means as generally applicable as infrared and Raman spectroscopy.

2.2. Historical Survey

The Raman effect is named after *Chandrasekhara Venkata Raman*[35], the Indian physicist who first observed the effect in the spring of 1928, following its prediction by *Smekal*[31], *Kramers* and *Heisenberg*[32], *Schrödinger*[33], and *Dirac*[34] in the years 1923 through 1927[35]. Shortly after its discovery a number of French and Russian authors also reported their work on this phenomenon[35a,35b]. Raman spectroscopy was born and immediately aroused the interest of many physicists and chemists. Infrared spectroscopy, which also provides information about vibrations of molecules, had been known since the beginning of the century[36], but measurement of the spectra was extremely difficult. Raman spectra, on the other hand, were more easily accessible. In nearly every spectrographic laboratory there was the necessary equipment for Raman spectroscopy: a mercury arc lamp and a prism spectrograph. However, the Raman effect is very weak, so Raman spectroscopy was not without its limitations. Exposure times of the order of a few hours to several days had to be used and, generally, only colorless liquids in amounts of a few milliliters could be investigated. Furthermore, the fluorescence of impurities can mask the Raman spectrum completely. Despite these difficulties, however, about 2000 papers dealing with Raman spectroscopy were published in the first decade after the discovery of the Raman effect[1]. They provided the basis for a great deal of our present-day knowledge of vibrational spectroscopy. After the second world war more efficient infrared spectrometers were developed, which were simple in operation and which provided spectra from milligram samples in any state. As a consequence, interest in Raman spectroscopy declined and until about 5 years ago Raman spectroscopy was not a widely used technique.

The steady development of laser light sources since 1960[37,38] has initiated a renaissance of Raman spectroscopy. Present-day Raman light sources have a spectral radiance that can be as much as 10 powers of ten higher than that of the mercury arc lamps used in the earlier days of Raman spectroscopy. Since the intensity of the scattered Raman radiation of a sample is proportional to the radiance of the light source, satisfactory Raman spectra can now be obtained with only one milligram to 1 microgram of substance in the liquid, solid or gaseous state. But in spite of the use of laser sources the Raman radiation remains weak: the radiant flux of a Raman band, excited by laser radiation is in the order of only 10^{-10} watt (cf. Section 2.4). Today one can also record Raman spectra of colored or fluorescent substances, if an exciting line is used which is far from the region of absorption of the substance. Today Raman spectroscopy is as readily

applicable as infrared spectroscopy for the study of molecular vibrations; currently, more than 1000 papers on Raman spectroscopy are being published each year.

2.3. Theory of Raman Spectroscopy

Raman spectra are produced by the interaction of light quanta with molecules. Light quanta have the properties of particles and of waves. Therefore the interaction can be explained in terms of classical physics both on the basis of the collision of a light particle with a molecule as well as the modulation of a light wave by the vibrations of a molecule.

During an *inelastic impact* of a light quantum with a molecule the vibrational energy can be transferred from the light quantum to the molecule or can be given from the molecule to the light quantum (Fig. 2a). The number of molecules in the first excited vibrational state N_s relative to the number in the vibrational ground state N_0 is given by the Boltzmann law (Figs. 2b and 2c):

$$N_s = N_0 \cdot e^{-\frac{h\nu_s}{kT}}. \qquad (1)$$

At 300 °K and a vibrational frequency of 1000 cm^{-1} only about 1 % of the molecules are in the first excited state. Therefore an inelastic impact of a light quantum with

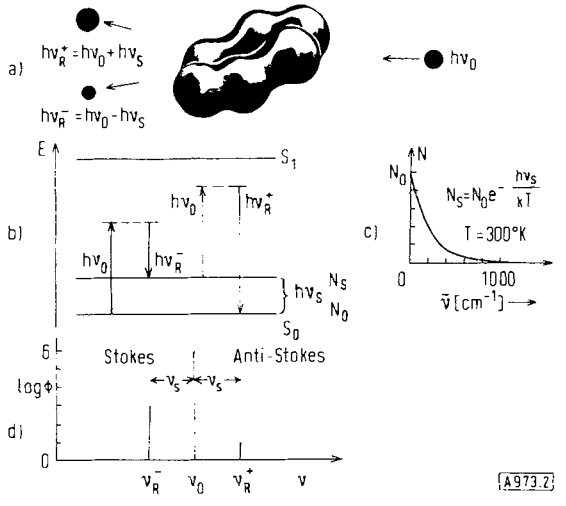


Fig. 2. Raman effect as inelastic impact of a light quantum with a molecule. a) impact process, b) energy level diagram, c) relative occupation of vibration level at $\tilde{\nu}$ cm^{-1} and 300 K, d) Stokes and anti-Stokes Raman spectra.

a molecule, in the course of which vibrational energy is given to the molecule, is approximately 100 times more probable than an inelastic impact in which the vibrational energy is transferred from the molecule to the light quantum. Normally, therefore, the more intense Raman spectrum on the long wavelength side of the exciting line (Fig. 2d), the so-called Stokes Raman spectrum[*], is observed. From the relative intensity of the Stokes and the anti-Stokes Raman lines one can calculate the vibrational temperature of the molecules [cf. eq. (10)].

[*] Stokes rule states that a fluorescence band is on the long wavelength side (at lower energies) of the absorption band of the substance. Application of this concept to Raman spectra is illogical [1], but common.

An elastic impact occurs with much greater probability than an inelastic impact. The former produces Rayleigh scattering at the frequency of the exciting radiation.

The absolute intensity of the vibrational bands in a Raman spectrum can be explained in terms of the *interaction* of a molecule with an electromagnetic *wave*. When a molecule is exposed to an electric field (Fig. 3), there will be a small shift of the center of the positive charges relative to the center of the negative charges. An induced dipole moment $\boldsymbol{\mu}'$ is created which is proportional to the electric field strength E and the "elasticity" of the charges in the molecule, *i.e.* the polarizability $\boldsymbol{\alpha}$:

$$\boldsymbol{\mu}' = \boldsymbol{\alpha}\mathbf{E} \qquad (2)$$

The polarizability of a molecule is generally greatest in the direction of the largest dimension of a molecule. The directional dependence of the polarizability is described by the components α_{ij} (i, j = x, y, z), which constitute the so called polarizability tensor.

$$\begin{aligned} \mu_x' &= \alpha_{xx}E_x + \alpha_{xy}E_y + \alpha_{xz}E_z \\ \mu_y' &= \alpha_{yx}E_x + \alpha_{yy}E_y + \alpha_{yz}E_z \\ \mu_z' &= \alpha_{zx}E_x + \alpha_{zy}E_y + \alpha_{zz}E_z \end{aligned} \qquad (3)$$

For non-chiral molecules this tensor is symmetrical, that is $\alpha_{ij} = \alpha_{ji}$, and therefore it has only 6 different components.

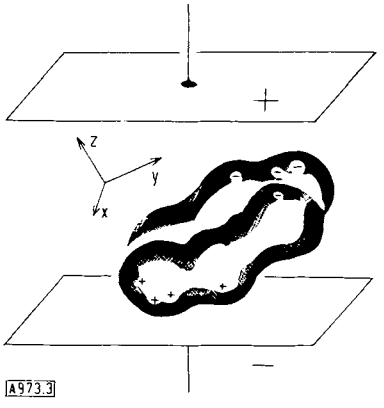


Fig. 3. Induced dipole moment of a molecule in an electric field.

If an alternating electric field is incident upon the molecule, the magnitude of the induced dipole moment will change with its frequency ν_0. Like a Hertz dipole the molecule will then emit radiation of the same frequency ν_0. This radiation is called the Rayleigh radiation.

If, at the same time, there is also mechanical vibration of the molecule, bonds will be compressed, stretched or

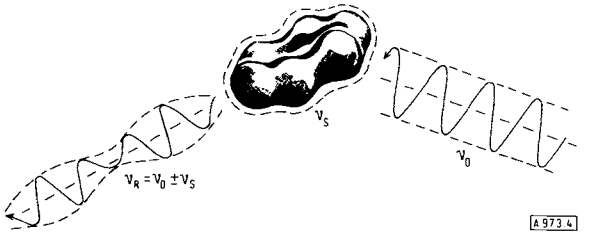


Fig. 4. Modulation of the scattered radiation of a vibrating molecule.

bent, during the course of which the coulombic attraction of the valence electrons by the nuclei will change with the frequency of the vibration. This means that the electron polarizability of the molecule will change with the frequency of the vibration. As a consequence the amplitude of the emitted wave will also change in phase with the mechanical vibration: The molecule emits—like an AM radio antenna—an amplitude-modulated electromagnetic wave (Fig. 4).

The classical description for this mechanism is as follows: The electric field strength of the exciting radiation changes with the frequency ν_0:

$$\mathbf{E} = \mathbf{E}_0 \cos 2\pi \nu_0 t \tag{4}$$

The polarizability tensor $\boldsymbol{\alpha} = (\alpha_{ij})$; i, j = x, y, z of the molecule, which is vibrating with a frequency ν_k, has two components: the unchanging polarizability, $\boldsymbol{\alpha}_0$, and a component that changes with the frequency ν_k:

$$\boldsymbol{\alpha} = \boldsymbol{\alpha}_0 + \left(\frac{\partial \boldsymbol{\alpha}}{\partial Q_k}\right)_0 \mathbf{A}_k \cos 2\pi \nu_k t \tag{5}$$

$Q_k = \mathbf{A}_k \cos 2\pi \nu_k t$ is called the normal coordinate, $\mathbf{A}_k$ describes the amplitude of the individual atoms during the normal vibration k. From eqs. (4) and (5) the induced dipole moment $\boldsymbol{\mu}' = \boldsymbol{\alpha}\mathbf{E}$ will be:

$$\boldsymbol{\mu}' = \boldsymbol{\alpha}_0 \mathbf{E}_0 \cos 2\pi \nu_0 t + \left(\frac{\partial \boldsymbol{\alpha}}{\partial Q_k}\right)_0 \mathbf{A}_k \mathbf{E}_0 \cos(2\pi \nu_0 t) \cos(2\pi \nu_k t) \tag{6}$$

This may be transformed into the following formula which describes the induced dipole moment of a molecule that performs a mechanical vibration of frequency ν_k and at the same time is exposed to an electromagnetic field of frequency ν_0:

$$\boldsymbol{\mu}' = \boldsymbol{\alpha}_0 \mathbf{E}_0 \cos(2\pi \nu_0 t) + \frac{1}{2}\left(\frac{\partial \boldsymbol{\alpha}}{\partial Q_k}\right)_0 \mathbf{A}_k \mathbf{E}_0 [\cos 2\pi(\nu_0 - \nu_k)t + \cos 2\pi(\nu_0 + \nu_k)t)] \tag{7}$$

The first term in eq. (7) describes the Rayleigh radiation with the frequency ν_0, the second the Stokes $(\nu_0 - \nu_k)$ and anti-Stokes Raman radiation $(\nu_0 + \nu_k)$.

The intensity of the Raman lines is proportional to the square of the change of the induced dipole moment and thus also to the square of the change of the polarizability, $(\partial\boldsymbol{\alpha}/\partial Q_k)_0^2$, during vibration of the atoms about their equilibrium position.

The prediction of eq. (7), that anti-Stokes and Stokes Raman lines should have the same intensity does not take into account the different population of the vibrational ground and excited states and is therefore not in accord with observation. Quantum mechanical treatment gives the right answer. On this basis *Placzek* was able to derive equations which accurately reproduce the observed intensities[39,40]. However, these expressions are valid only in the case where excitation of the Raman effect is effected in a spectral region far away from absorption bands of the molecule, *i.e.* when there is no "resonance Raman effect". The Raman scattering coefficient, for an oriented molecule or a unit cell of a crystal, is, for the Stokes Raman radiation:

$$S^-_{k,rr'} = \frac{2\pi^2 h}{c} \cdot \frac{(\tilde{\nu}_0 - \tilde{\nu}_k)^4}{\tilde{\nu}_k [1 - \exp(-hc\tilde{\nu}_k / kT)]} \cdot g_k \left(\frac{\partial \alpha_{rr'}}{\partial Q_k}\right)_0^2 \tag{8}$$

and for the anti-Stokes radiation:

$$S^+_{k,rr} = \frac{2\pi^2 h}{c} \cdot \frac{(\tilde{\nu}_0 + \tilde{\nu}_k)^4}{\tilde{\nu}_k [\exp(hc\tilde{\nu}_k / kT) - 1]} \cdot g_k \left(\frac{\partial \alpha_{rr'}}{\partial Q_k}\right)_0^2 \tag{9}$$

It is assumed here that the electric vector of the exciting radiation is parallel to one axis r of a molecularly- or crystallographically-fixed Cartesian coordinate of the molecule or crystal, and the electric vector of the observed Raman radiation is parallel to r'; $\tilde{\nu}_0$ and $\tilde{\nu}_k$ are the frequencies of the exciting radiation and the vibration (in wave number units, cm^{-1}), T is the absolute temperature of the sample, g_k is the degree of degeneracy and $(\partial\alpha_{rr'}/\partial Q_k)_0$ is the change in the component $\alpha_{rr'}$ of the polarizability tensor by the normal vibration k. The order of magnitude of the Raman scattering coefficients is 10^{-28} cm^2·molecule^{-1}·sr^{-1}. The intensity ratio of anti-Stokes to Stokes Raman bands is, according to eqs. (8) and (9):

$$\frac{S^+_k}{S^-_k} = \frac{(\tilde{\nu}_0 + \tilde{\nu}_k)^4}{(\tilde{\nu}_0 - \tilde{\nu}_k)^4} \cdot e^{h\nu/kT}. \tag{10}$$

Calculation of the scattering coefficient for molecules in gases or liquids requires use of the mean value $\bar{\alpha}'$ and of the anisotropy γ' of the change of polarizability by a normal vibration k:

$$\bar{\alpha}' = \tfrac{1}{3}(\alpha'_{xx} + \alpha'_{yy} + \alpha'_{zz}) \tag{11}$$

$$\gamma'^2 = \tfrac{1}{2}[(\alpha'_{xx} - \alpha'_{yy})^2 + (\alpha'_{yy} - \alpha'_{zz})^2 + (\alpha'_{zz} - \alpha'_{xx})^2 + 6(\alpha'^2_{xy} + \alpha'^2_{xy} + \alpha'^2_{xz})] \tag{12}$$

Here $\alpha_{rr'} = (\delta\alpha_{rr'}/\delta Q)_0$; in all the terms a subscript k has been left out.

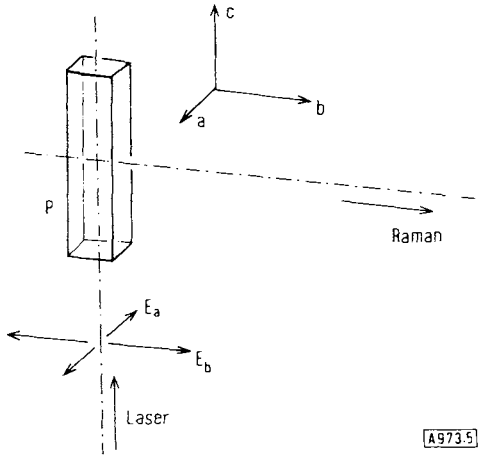


Fig. 5. Measurement of the degree of depolarization of the Raman radiation on excitation with a laser light-source.

If, according to Figure 5, the substance is illuminated by polarized exciting light in the direction of the c axis and if one observes without an analyzer the Raman radiation emitted in the b direction, two scattering coefficients must be taken into consideration: $S_{\parallel}$ for the electric vector of the exciting radiation parallel to the direction of the observation b and $S_{\perp}$ for the electric vector of the exciting radiation perpendicular to the direction of observation, *i.e.* parallel to the a axis:

$$S_{k\parallel}^{-} = \frac{2\pi^2 h}{c} \frac{(\tilde{\nu}_0 - \tilde{\nu}_k)^4}{\tilde{\nu}_k[1-\exp(-hc\tilde{\nu}_k/kT)]} g_k \frac{6}{45}\gamma_k'^2 , \quad (13)$$

$$S_{k\perp}^{-} = \frac{2\pi^2 h}{c} \frac{(\tilde{\nu}_0 - \tilde{\nu}_k)^4}{\tilde{\nu}_k[1-\exp(-hc\tilde{\nu}_k/kT)]} g_k \left(\bar{\alpha}_k'^2 + \frac{7}{45}\gamma_k'\right)^2 . \quad (14)$$

The ratio of the two scattering coefficients is called the degree of depolarization $\rho_{k,n}$:

$$\rho_{k,n} = \frac{S_{k\parallel}}{S_{k\perp}} = \frac{6\gamma'^2}{45\bar{\alpha}'^2 + 7\gamma'^2} . \quad (15)$$

Normal vibrations which are symmetric with respect to all symmetry elements of a molecule—totally symmetric vibrations—may modulate all components of the polarizability tensor and therefore also $\bar{\alpha}'$ and γ'. Hence[*],

$$0 \leqq \rho_{k,n} \leqq 6/7 \quad (16)$$

For totally symmetric vibrations of molecules with cubic symmetry $\gamma' = 0$, and therefore

$$\rho_{k,n} = 0 \quad (17)$$

In the case of vibrations which are antisymmetric with respect to any symmetry element, however, $\bar{\alpha}' = 0$ and

$$\rho_{k,n} = 6/7 \quad (18)$$

In the Raman spectra of liquids or gases the totally symmetric normal vibrations can be determined by measuring the degree of depolarization.

To illustrate the activity of normal vibrations in the Raman and infrared spectrum let us consider the CO_2 molecule. The CO_2 molecule is capable of performing two stretching vibrations of the CO bonds: the symmetric (ν_s) and antisymmetric (ν_a) stretching vibrations:

Figure 6 shows schematically the change of the electron system as a consequence of these vibrations. For the symmetric stretching vibration ν_s of the CO_2 molecule both CO bonds are stretched or compressed at the same time (Fig. 6a). The coulombic attraction of the valence electrons by the atomic nuclei will change its magnitude with the frequency of the vibrations. Consequently the polarizability α of the CO_2 molecule will also change. The symmetric stretching vibration will thus be Raman active.

The dipole moment of the whole molecule remains equal to 0 because both dipole moments of the CO bonds are, at any one time, antiparallel and equal. A normal vibration

[*] If the Raman radiation is observed through an analyzer, equations (13)—(18) are changed; for example, in (16) and (18) 3/4 should replace 6/7 [4, 40].

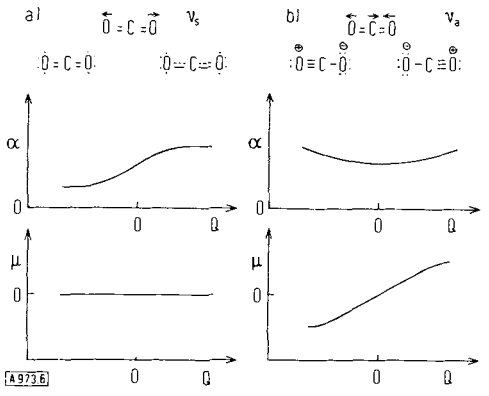


Fig. 6. Change of the polarizability α and the dipole moment μ of a) the symmetric, and b) the antisymmetric stretching vibration of the CO_2 molecule.

can be excited by radiation from the infrared region only if it changes the molecular dipole moment. Consequently the symmetric stretching vibration is infrared inactive.

For the antisymmetric stretching vibration of the CO_2 molecule everything is just the other way round: The polarizabilities of both states of the molecule shown in Figure 6b are of equal magnitude. For the position of the equilibrium with $Q=0$ also $(\partial\alpha/\partial Q_k)_0 = 0$. This vibration is not Raman active. The dipole moments of the two CO bonds are no longer equal in magnitude and the molecule as a whole has a dipole moment that changes its direction in rhythm with the vibration. The antisymmetric stretching vibration of the CO_2 molecule is therefore infrared active.

The CO_2 molecule provides us with a simple example for illustrating an important selection rule, *the rule of mutual exclusion:* If a molecule has a center of symmetry, then all vibrations symmetric with respect to this center of symmetry are forbidden in the infrared spectrum, and all vibrations which are antisymmetric with respect to the center of symmetry are forbidden in the Raman spectrum. Here, the term "forbidden" means that the mechanical vibrations are not observable as bands in the IR or Raman spectrum respectively.

The possible vibrations of the molecules may be divided into symmetry species, according to their symmetry or antisymmetry with respect to the symmetry elements of the molecule. The infrared or Raman activity of these species is given by so called "character tables"[1-6] which have been obtained by the rules of group theory. By counting the number of vibrations which are shown only in one of both spectra and those which show up in both spectra, one can often ascertain the symmetry properties of a molecule. This is facilitated by measurement of the degree of depolarization of the Raman lines, from which the total symmetric vibration can be recognized immediately.

2.4. Raman Spectrometers with Laser Light Sources

The laser principle (*l*ight *a*mplification by stimulated *e*mission of *r*adiation) allows the construction of light sources, the spectral radiance of which is not—as is the case in "classical" light sources like the sun and the mercury arc

lamp—limited by the temperature according to Planck's radiation law. By a "pumping" process more atoms, ions or molecules of the active substance are brought into an excited state of the electron system than there are in a state of lower energy which may be reached by emission of light quanta $h\nu$. Due to this inversion of the population of the states in the active substance it has the properties of an amplifier for light of frequency ν by stimulated emission. If the active substance is enclosed between highly reflecting mirrors coherent light beams of high spectral radiance may be produced. There are some noble gas lasers (He-Ne, Ar^+, Kr^+ lasers) which may be used as light sources for Raman spectroscopy. These give continuous waves and produce monochromatic and completely polarized light in all regions of the visible spectrum. Their spectral radiance (radiant flux per solid angle, area and spectral band width) is higher by as much as 10 powers of 10 compared to the mercury arc lamp.

The radiant flux of Raman radiation scattered by a sample is proportional to the spectral radiance of the light source. It is possible therefore not only to reduce the amount of sample required for recording a Raman spectrum by three powers of 10 from the gram to the milligram region but also to record spectra with a higher signal-to-noise ratio, at a higher recording speed and using a lower concentration of the substance, than was possible with the earlier mercury arc spectrometers.

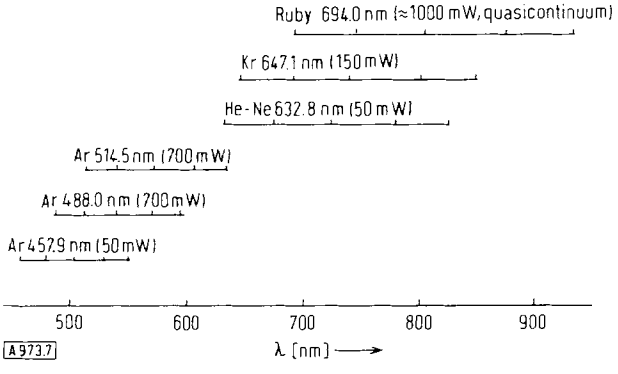


Fig. 7. Range of the Raman spectrum by excitation with different laser light-sources. The scale under the name of the laser light-source is marked 0 –3700 cm^{-1} (divisions 0, 1000, 2000, 3000, 3700 cm^{-1}).

Figure 7 shows the wavelengths of some lasers used for Raman spectroscopy and the region of the Stokes Raman spectrum excited by them. The intensity of the Raman lines is approximately proportional to the fourth power of the frequency of the exciting line ["ν^4-law". eq. (12), (13)]; therefore, it is advisable to use exciting light of a high frequency (*i.e.* short wavelength), for example the strong lines of the argon laser in the blue and green region of the spectrum (488 and 515 nm). For colored substances, which show absorption bands in this region, it is in most cases not possible to record a Raman spectrum. The exciting radiation is absorbed by the substance, and as a result the substance is heated, vaporized or decomposed. Often one can then use another exciting line from a spectral region, for instance the red, in which there is no absorption by the substance. At the same time possible interference of the Raman spectrum by the fluorescence spectra of impurities may be reduced when exciting light of longer wavelength is used. However, the use of laser light sources in the red region of the spectrum is not generally advisable, not only because of the ν^4-law but also because the radiation detectors for this spectral region are of lower sensitivity compared to those for the blue-green region of the spectrum. It is preferable therefore to have one laser (argon laser) for the blue and another laser (krypton laser) for the red region of the spectrum.

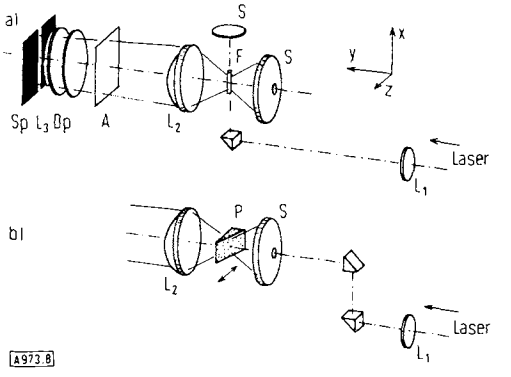


Fig. 8. Sample arrangements in a Raman spectrometer with laser light-source: a) for transparent samples, b) for crystal powders.

The most satisfactory arrangement for illumination of the sample in a Raman spectrometer furnished with a laser light source is to place the sample at the focus of the laser beam[41] (Fig. 8a). This yields a high radiation intensity in a small sample. Depending on the focal length of the focusing lens L_1[42], the diameter of the beam near the focus is in the order of 10 ... 100 μm. The narrow cylinder-like part of the sample illuminated by the laser is imaged into the entrance slit Sp of a monochromator by means of a high-power magnifying lens L_2. In front of the monochromator there is usually an analyzer A, for measurement of the degree of depolarization of the Raman lines, and a "polarization scrambler" Dp which reduces falsification of this measurement by the polarizing effect of the gratings in the monochromator. The amount of sample to be used in such an arrangement is determined by the volume of a tube which is large enough to enclose the laser beam in the region of the focus and which has a length H of about 2 ... 5 mm, so as to fully illuminate the whole length of the entrance slit of the monochromator. The mirrors S increase the radiant flux, from the exciter, and the Raman radiation.

For the optical setup shown in Figure 8a, without mirrors S, the radiant flux of a Raman line (watt) "seen" by the lens L_2 is approximately given by:

$$\Phi_k = \Phi_0 \cdot S_k \cdot N \cdot H \cdot L \cdot 4\pi \sin^2(\alpha/2) \qquad (19)$$

Φ_0 is the radiant flux of the exciting radiation within the sample (watt), S_k is the Raman scattering coefficient according to equations (8), (9), (12) and (13), N is the number of molecules (or unit cells respectively) per cm^3, H is the length of sample used, L is a factor, which takes into account the influence of the refractive index and the internal field effect of the sample[4, 43] and α is the half

angle of the light beam, seen by lens L_2. For a Raman scattering coefficient of about $10^{-28} \ldots 10^{-30}$ cm^2·molecule^{-1}·sr^{-1}, according to eq. (19)—taking into account the transmittance of the monochromator and the spectral slit width—and a laser of radiant flux about 1 watt, only about 10^{-9} to 10^{-11} watts is available when a Raman line is recorded by the spectrometer. The limit of detection of a photomultiplier is in the order of 10^{-16} watts[15].

If one could dispense with sample cells an amount of sample in the order of some thousandths of a cubic millimeter would be sufficient for Raman spectroscopy. However, for convenience of handling, a few milligrams of sample are normally used. Melting-point capillaries are often adequate as cells for Raman spectroscopy. Spectra of all transparent substances may be recorded with the arrangement shown in Figure 8a: liquids, solutions, gases. This arrangement is also suitable for recording the Raman spectra of crystal needles, filaments, and single crystals. By irradiation of the sample with the laser beam in different directions and by using different directions of polarization of laser beam and Raman radiation up to six different Raman spectra may be recorded. From such measurements the symmetry species of the vibrations and also the arrangement of the molecules in a crystal may be deduced (cf. Section 3.6).

Because of multiple reflections and normal and double refractions by the crystallites neither the intensity nor the polarization of the Raman lines in the spectra of crystal powders show any dependence on direction. Moreover, since the exciting radiation undergoes multiple reflections and refractions within the sample, a high amount of this "unshifted" radiation is mixed with the Raman radiation, which is about 5 to 10 powers of 10 weaker. The unshifted radiation produces stray light within the spectrometer, which may mask the Raman spectrum completely (see below).

By suitable preparation and alignment of the sample this stray light may be diminished. Crystal powders may be so arranged that either the "transmitted" or the "reflected" radiation will be analyzed[44]. The angle between the exciting radiation and the Raman radiation to be analyzed is then 0 or 180° respectively. The theory of the balance of Raman radiation from crystal powders[45], which is similar to the Kubelka-Munk theory[46,47], shows that the 0° arrangement is superior to the 180° arrangement, since it gives only 1/10 to 1/1000 of the intensity of the unshifted radiation. Both arrangements give Raman radiation of about the same intensity. The optimal thickness[48] of the sample for maximum Raman intensity can readily be found by shifting the sample sideways in a wedge-shaped cell P (see Fig. 8b). The intensity of the Raman spectrum of crystal powders is greater when the size of the crystallites is larger or when the powder is pressed into a disk[49,50]. If however the sample absorbs in the region of the exciting line it is, according to theory[45], more suitable to use the 180° arrangement. Decomposition of an absorbing sample by the laser beam can be avoided by rotation of the sample[51].

Even when the optimum arrangement of sample has been achieved the Raman light to be analyzed is mixed with unshifted light that is more intense by three to eight powers of ten. A good monochromator reduces the false light by about 5 powers of 10. Therefore one has to use double or even triple monochromators, only one of which effects the spectral dispersion; the others are—rather expensive—filters. They may be replaced by small band interference filters or resonance absorption filters. For example, we have built a simple Raman spectrometer in which a single monochromator is coupled with an interference filter in a triple reflection arrangement[52]. The exciting line is reduced selectively by the interference filter by 5 powers of 10. Iodine vapor may be used as absorption filter for the line of the argon laser near 514.5 nm[53,54]. Technical details of monochromators, radiation detectors, amplifiers and recording equipment have been described elsewhere[14,15,23].

3. Applications

3.1. Experimental Possibilities of Raman Spectroscopy

Until recently the application of vibrational spectroscopy was largely determined by the experimental conditions of infrared spectroscopy; Raman spectroscopy renders some kinds of measurements easier and offers new possibilities[55]:

1. The whole frequency region (10 ... 4000 cm^{-1}) of molecular and lattice vibrations is covered with *one* instrument.

2. The amount of sample needed is in the milli- to microgram region. Raman spectra of gas-chromatographic samples in the order of 1 nl and of crystals of less than 1 μg have been recorded[56,56a,57].

3. Water shows only a very weak Raman spectrum and is therefore suitable as solvent. Infrared spectroscopy of solutions in water is very difficult because of the very strong continuous absorption bands and the solubility of most window materials.

4. The intensity of the Raman lines of a substance is proportional to the concentration. It can be measured acurately over a range of about 4 powers of ten.

5. Simple glass vessels, *e.g.* melting-point capillaries, are suitable as sample cells. Sensitive, reactive or precious substances may be analyzed in their sealed containers (*e.g.* ampules) without decomposition and without loss.

6. The Raman spectra of samples at high temperatures (molten salts[13,59-61], flames[62,63]) and near the absolute zero[64,65] can been recorded.

7. The matrix-isolation technique[66,68] allows the investigation of unstable molecules such as the noble gas compounds[69,70], of monomeric dihalides of elements of the 4th main group[71,72], of products from plasma reactions[73], and of conformational isomers[74], as well as the determination of the isotopic structure of vibration bands[75].

8. The use of pulsed lasers as light sources makes it possible to measure Raman spectra within a few milliseconds, *i.e.* very fast reactions can be investigated[58].

9. Intermolecular interactions may be studied by application of high pressures[76-78] or by using adsorbed substances[79-83].

10. The determination of contaminants in air and of the temperature of the atmosphere would seem possible over distances of some km with a laser-radar[84–89].

11. Contrary to all expectations, the recording of Raman spectra of highly absorbing substances such as silicon[90], Fe_2O_3, and CrO_3[91] as well as black substances like graphite and coal[92–94] is possible.

Two examples will suffice to demonstrate the applicability of Raman spectroscopy to the non-destructive analysis of precious substances and to production control respectively. In both cases Raman spectra have been recorded on samples in their original ampules as supplied by the manufacturer. Figure 9 shows the Raman spectrum of

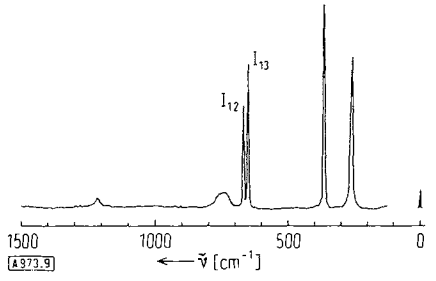


Fig. 9. Raman spectrum of chloroform 57.6% labeled with ^{13}C; in original ampoule. Evaluation of the band pair near 670 cm^{-1} yields $I_{13}/(I_{12}+I_{13})=58.7\%$ ^{13}C.

^{13}C-labeled chloroform (1 ml ampule), which according to the manufacturer is 57.6% enriched with ^{13}C. The symmetric C—Cl stretching vibration near 670 cm^{-1} is split into two components, which are to be assigned to the molecules with ^{12}C- and ^{13}C-atoms respectively. An evaluation of the relative intensity of these bands (as measured by peak height) gives a ^{13}C content of 58.7%. Figure 10a shows the Raman spectrum of crystallized luminal, and Figure 10b that of a 20% solution of luminal in

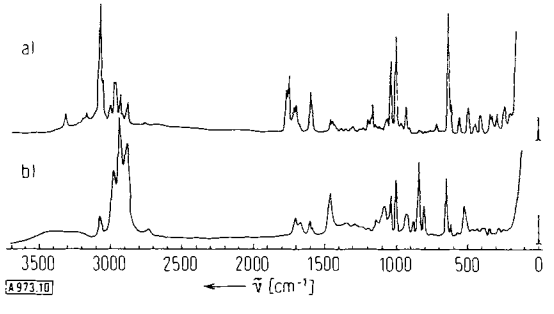


Fig. 10. Raman spectra of a) crystalline luminal, b) a 20% solution of luminal in propyleneglycol, ethanol and water in original ampule (Merck).

a mixture of propylene glycol, ethanol, and water (original ampule). The solvents give rise to bands in the spectrum at 2800—3000 cm^{-1} (C—H stretching vibration), at 1460 cm^{-1} (C—H bending vibration), and at 800—850 cm^{-1} (C—C stretching vibration); the vibrations of the CO and OH groups give only weak bands at 1080 and 3400 cm^{-1}. This non-destructive method of analysis permits simultaneous combination of the qualitative and quantitative analysis by Raman spectroscopy with the determination of fluorescing compounds (by measurement of the "background") and of colloidal particles (by the measurement of Tyndall scattering).

By coupling Raman spectrometers with computers the applications of Raman spectroscopy can be improved and extended, *e.g.* as regards the measurement of integral intensities, compensation of the properties of the spectrometers[95–97], resolution of overlapping bands[98], measurement of extremely weak spectra by multi-scan averaging[99–101], multiple component analysis[102], and the determination of characteristic bands for the elucidation of structure[103].

3.2. Potentialities of the Combination of Raman with Infrared Spectroscopy

A complete understanding of the vibrational spectra of a compound can give considerable information about bond strengths, molecular shapes, *etc.* The molecular vibration frequencies obtained from Raman spectra are to a great extent the same as those obtainable from infrared spectra. However, depending on symmetry, some frequencies in the Raman spectrum are absent in the infrared spectrum and *vice versa* (see Table 1).

Table 1. General overview of vibrational spectroscopy.

Characteristic features of the vibration spectrum	Properties of molecules or Bravais unit cells
Number of normal vibrations z	Number of atoms n, $z=3n-6$, for linear molecules $z=3n-5$
Frequencies	Masses of atoms, geometry, force constants (elastic properties of bonds)
Intensities in the infrared spectrum	Change in properties of the electron system with changing position of atoms change of dipole moment
Raman spectrum	change of polarizability
	IR and Raman activities are dependent on the symmetry of the vibrations and the molecules or Bravais cells

From Table 1 it is at once apparent that Raman spectroscopy and infrared spectroscopy are complementary methods which, when used in combination, provide considerable information about the molecules of the substance under examination:

The frequencies as well as the intensities of the vibrations are determined by the most important parameters of the molecular structure; therefore, both spectra may be used as "fingerprints" for the identification of molecules.

Structural units of molecules may also be identified by their characteristic frequencies and intensities. Generally the vibrations of polar groups and antisymmetric vibrations of atomic groups are stronger in the infrared spectrum because the dipole moment is strongly modulated, whereas vibrations of nonpolar groups and molecular skeletons and total symmetric vibrations are often stronger in the Raman

spectrum, since they strongly modulate the polarizability of the molecule.

From a comparison of infrared and Raman spectra the symmetry of molecules and the structure of isomers may be determined.

On the one hand, calculation of the frequencies and intensities of both spectra provides data about bond orders as well as about the polarities and polarizabilities of bonds, while, on the other, from a comparison of measured and calculated spectra the structures of unknown compounds may be determined. Finally, infrared and Raman spectra also provide data about intermolecular interactions and about the symmetry and structure of complexes, macromolecules or crystals. Particularly valuable here are measurements with polarized radiation.

Examples of such applications are discussed in the following paragraphs.

3.3. Characteristic Bands in the Raman Spectrum

For most vibrations of a molecule several bonds or angles are deformed simultaneously. However, a vibration may be localized in one group of the molecule when the vibrational frequency of this group, taken as isolated oscillator, is different from the frequencies of neighboring groups. In this case the frequencies and intensities of the vibration in the infrared and Raman spectrum are characteristic for this group, *i.e.* the vibration is independent of the rest of the molecule and may therefore be useful for detection of the group.

Characteristic frequencies in infrared spectra were first established by *Coblentz* in 1905[36]. Numerous publications contain tables of characteristic infrared bands. In some cases the intensity of these bands in the Raman spectrum is also discussed, both for organic compounds[6, 104, 105] as well as for inorganic compounds[106–108]. Some publications deal especially with Raman spectroscopic data[1, 7, 8, 109, 110]. Table 2 shows some characteristic bands, which may be used for investigations using the Raman spectrum alone or a combination of Raman and infrared spectra.

The infrared and Raman spectra of cystine (Fig. 11) show clearly the complementary nature of the two spectra. The infrared spectrum shows, in the region of 3000 cm^{-1}, the broad band of the NH_3^+ stretching vibrations of the zwitterionic form. In the Raman spectrum, on the other hand, only the CH (2915 cm^{-1}) and CH_2 stretching vibrations (ν_s: 2915, ν_a 2970 cm^{-1}) are to be seen in this region. In the infrared spectrum the NH_3^+ bending vibration and the antisymmetric stretching vibration ν_a (CO_2^-) appear at about 1600 cm^{-1}. Both are weak in the Raman spectrum, whereas the symmetric stretching vibration ν_s (CO_2^-) at 1410 cm^{-1} is strong both in the infrared and in the Raman spectrum. The strongest Raman band, 497 cm^{-1}, is very weak in the infrared spectrum; it may be assigned to the stretching vibration of the non-polar S—S bond, ν(SS). The position and intensity of this band, together with the ν(CS) near 680 cm^{-1}, can be used for determining the conformation of the disulfide bridges in proteins[111].

Table 2. Characteristic frequencies and Raman and infrared intensities of groups in organic compounds.

Vibration [a]	Region [cm^{-1}]	Intensity [b] Raman	IR
ν(O—H)	3650—3000	w	s
ν(N—H)	3500—3300	m	m
ν(≡C—H)	3300	w	s
ν(=C—H)	3100—3000	s	m
ν(—C—H)	3000—2800	s	s
ν(—S—H)	2600—2550	s	w
ν(C≡N)	2255—2220	m—s	s—0
ν(C≡C)	2250—2100	vs	w—0
ν(C=O)	1820—1680	s—w	vs
ν(C=C)	1900—1500	vs—m	0—w
ν(C=N)	1680—1610	s	m
ν(N=N), aliph. subst.	1580—1550	m	0
ν(N=N), arom. subst.	1440—1410	m	0
ν_a((C—)NO_2)	1590—1530	m	s
ν_s((C—)NO_2)	1380—1340	vs	m
ν_a((C—)SO_2(—C))	1350—1310	w—0	s
ν_s((C—)SO_2(—C))	1160—1120	s	s
ν((C—)SO(—C))	1070—1020	m	s
ν(C=S)	1250—1000	s	w
δ(CH_2), δ(CH_3)	1470—1400	m	m
δ$_s$(CH_3)	1380	m—w, s, if at C=C	s—m
ν(CC), aromatics	1600, 1580	s—m	m—s
	1500, 1450	m—w	m—s
	1000	s (in mono-; *m*-; 1,3,5-derivatives)	0—w
ν(CC), alicyclics, aliph. chains	1300—600	s—m	m—w
ν_a(C—O—C)	1150—1060	w	s
ν_s(C—O—C)	970—800	s—m	w—0
ν_a(Si—O—Si)	1110—1000	w—0	vs
ν_s(Si—O—Si)	550—450	vs	w—0
ν(O—O)	900—845	s	0—w
ν(S—S)	550—430	s	0—w
ν(Se—Se)	330—290	s	0—w
ν(C(arom.)—S)	1100—1080	s	s—m
ν(C(aliph.)—S)	790—630	s	s—m
ν(C—Cl)	800—550	s	s
ν(C—Br)	700—500	s	s
ν(C—I)	660—480	s	s
δ$_s$(CC), aliph. chains			
C_n, $n=3\ldots12$	400—250	s—m	w—0
$n>12$	2495/*n*		
Lattice vibrations in molecular crystals (librations and translational vibrations)	200—20	vs 0	s—0

[a] ν stretching vibration, δ bending vibration, ν_s symmetric vibration, ν_a antisymmetric vibration.

[b] vs very strong, s strong, m medium, w weak, 0 very weak or inactive.

The stretching vibration of a C=C double bond is generally very weak in the infrared spectrum (sometimes it is for-

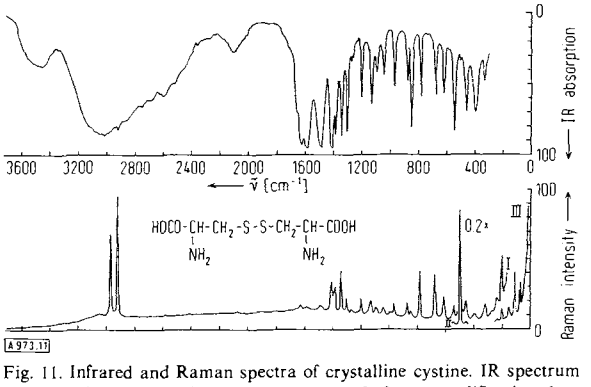


Fig. 11. Infrared and Raman spectra of crystalline cystine. IR spectrum of 0.8 mg in 400 mg KI; Raman spectrum I, 2 mg, amplification 1×; II, 2 mg, amplification 0.2×; III, disk, 140 mg, amplification 0.3×.

bidden), but may be easily recognized by its large intensity in the Raman spectrum. Table 3 shows the frequencies of isolated C=C double bonds with different substituents and bond angles. The strong dependence of the frequency of the C=C stretching vibration (1525—1875 cm^{-1}) on the substituents in cyclopropene derivatives is remarkable. This is not due to a change in the C=C force constants, but to a vibrational coupling with the neighboring bonds. When two oscillators of different frequencies are coupled the higher frequency will be shifted to higher values, the lower frequency to lower values, the shifts being greater the closer the frequencies of the isolated oscillators. Hence, the ν(C=C) of cyclopropenes is shifted to smaller frequencies when CH and especially when CD neighboring groups are present, and to higher frequencies when C—CH_3 groups are present.

The infrared spectrum of a compound, which was prepared by *Scharf* and *Seidler*, and which was known to have the molecular formula $C_6H_6OCl_2$ but was of unknown structure, (Fig. 12) showed only one band characteristic

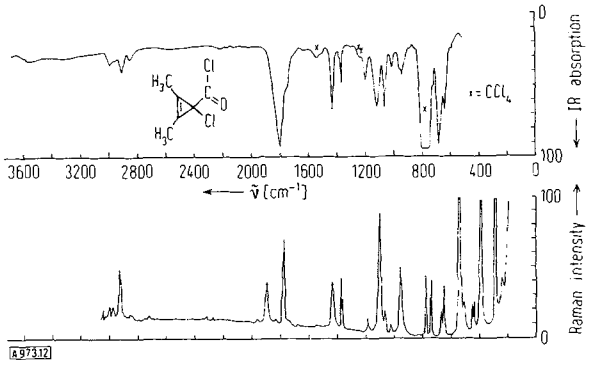
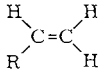
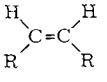
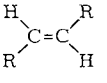
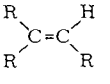
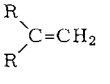


Fig. 12. IR and Raman spectra of 1-chloro-2,3-dimethyl-2-cyclopropene-1-carbonyl chloride ($C_6H_6OCl_2$). Infrared spectrum of the solution in CCl_4, Raman spectrum of the liquid substance.

of an acid chloride group at 1795 cm^{-1} in the region of the double bond frequencies. The Raman spectrum, however, showed, in addition to this band, another band at about 1898 cm^{-1}, which suggested the presence of a substituted cyclopropene ring. The structure tentatively

Table 3. Characteristic frequencies of C=C double bonds in hydrocarbons.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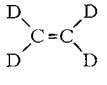
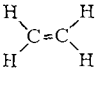
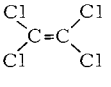
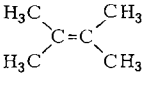
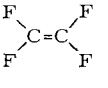
R = Alkyl	1641	1654	1667	1666	1648
					
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		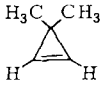	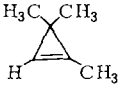	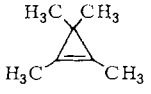	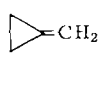
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		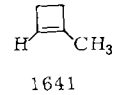	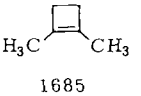	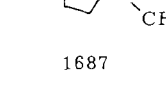	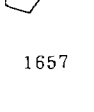
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	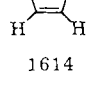	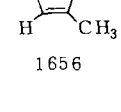	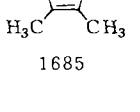	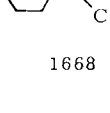	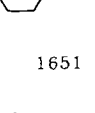
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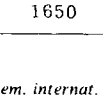
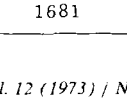
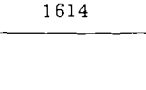
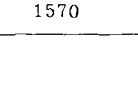
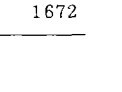
					
	1649	1678	1685	1668	1651
	1650	1681	1614	1570	1672

assigned to the compound is shown in Figure 12; this assignment was later proved correct[112]. The change of dipole moment by the C=C stretching vibration of this compound is obviously nearly 0. For other cyclopropane derivatives this vibration may be observed not only in the Raman, but also in the infrared spectrum (Fig. 13: 1,2,3-triphenylcyclopropene, ν(C=C): 1825 cm^{-1})[113]. Since the C=O- and the C=C-groups of 1-chloro-2,3-dimethyl-2-cyclopropene-1-carbonyl chloride (Fig. 12) are not conjugated, the vibrations of these groups behave as those of independent oscillators.

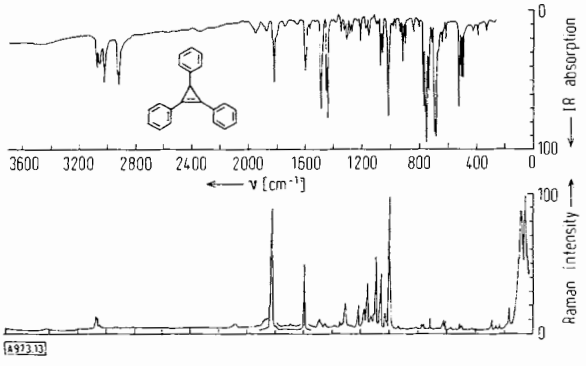
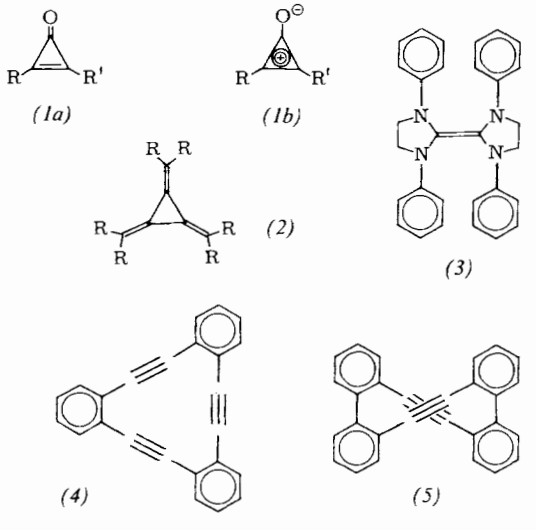


Fig. 13. Infrared and Raman spectra of crystalline 1,2,3-triphenylcyclopropene.

This is not so in the case of the cyclopropenones *(1)*. Here an investigation of the infrared and Raman spectra[114] and a calculation of the vibrational frequencies[115] showed that a band occurring at about 1610 cm^{-1} must be assigned to an in-phase vibration of both double bonds in the cyclopropenone system and a band near 1840 cm^{-1} to an out-of-phase vibration. Both vibrations are very strong in the infrared spectrum; in the Raman spectrum, however, the in-phase vibration is much stronger than the out-of-phase vibration. Analysis of the spectra would suggest participation of the zwitterionic structure *(1b)*, which would also explain the surprising stability of compound *(1)*.

The symmetric stretching vibration of the three-membered aromatic ring in triphenylcyclopropenylium bromide gives rise to a band near 1840 cm^{-1} in the Raman spectrum



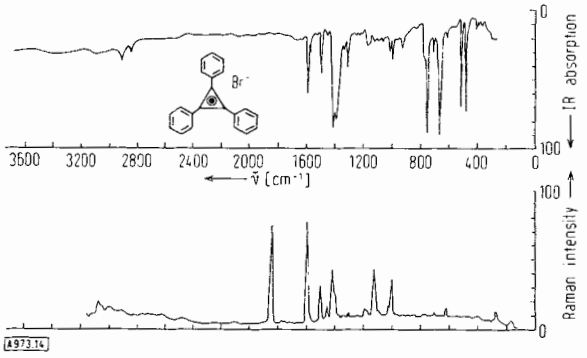


Fig. 14. Infrared and Raman spectra of crystalline triphenylcyclopropenylium bromide.

(Fig. 14). The infrared spectrum shows no trace of a band near this frequency. This is proof for the cyclopropenylium ion having a planar structure with a threefold symmetry axis, in which case the total symmetric vibrations are forbidden in the infrared spectrum, *i.e.* for the D_3 point group of the molecule[115,122]. The unsymmetric (degenerate) stretching vibration of the ring system shows a strong band near 1410 cm^{-1} both in the infrared and in the Raman spectrum. According to frequency calculations the force constants of the bonds in the cyclopropenylium ion are larger than those of the bonds in benzene[115,122]. The structure of the hexamethyl[3]radialene *(2)*, R = CH_3, has been established by observation of a strong Raman band of the ν_s(C=C) near 1880 cm^{-1} and absence of infrared bands of the same frequency[116]. Identification of the central double bond in compound *(3)* was also possible by observation of the ν(C=C) band (near 1640 cm^{-1}) in the Raman spectrum[117].

The stretching vibration of the N=N double bond in azo compounds is forbidden in the infrared spectrum if it is situated at the center of a centrosymmetric compound such as *trans*-azobenzene. However, *Lüttke* has been able to show by the frequency shifts introduced by ^{15}N-labeling that unsymmetric aromatic azo compounds exhibit a weak ν(N=N) in the infrared spectrum in the region 1410 ... 1440 cm^{-1}[118].

N=N stretching vibrations normally lead to medium or strong bands in the Raman spectrum[26,119]. This vibration appears at about 1520 cm^{-1} in the Raman spectra of mixed aromatic-aliphatic azo compounds (Fig. 15a); in the case of aliphatic azo compounds it is to be found near 1570 cm^{-1} (Fig. 15b)[120,121].

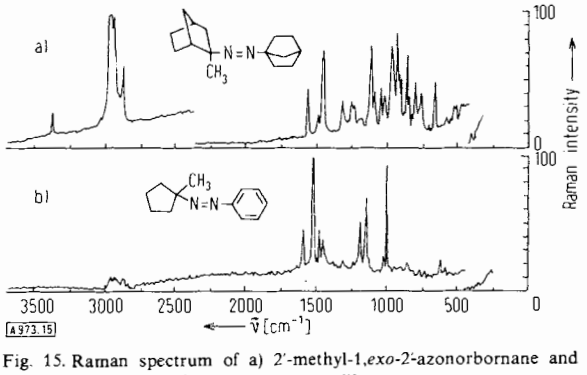


Fig. 15. Raman spectrum of a) 2'-methyl-1,*exo*-2'-azonorbornane and b) (1-methylcyclopentylazo)benzene, crystalline.

The stretching vibration of the C≡C grouping gives rise, if at all, to very weak bands in the infrared spectrum. Since the change in polarizability of this electron-rich group during vibration is large, it shows very strong bands in the Raman spectrum. Consequently, this group can be located very easily, even in large molecules like the steroids[124,125]. The Raman spectra of haloacetylenes have been studied by *Klaboe et al.*[126]. *Staab et al.* have investigated the properties of molecules containing several narrowly adjacent C≡C bonds. The Raman spectra showed that the C≡C bonds of the cyclododecatriyne *(4)* and -diyne *(5)* show a normal vibration frequency of 2220 cm^{-1}[127-130], and thus that there is no detectable mutual perturbation of these bonds.

The polar —C≡N-group can usually be recognized by a strong characteristic band in the infrared spectrum at 2100...2300 cm^{-1}[123]. If there is an electronegative substituent on the neighboring C-atom, then the change of dipole moment of the molecule by the C≡N vibration is so small that a band may not be seen in the infrared but only in the Raman spectrum[131,110]. Figure 16 shows as an example the infrared and Raman spectra of (1-cyanoethyl) acetate.

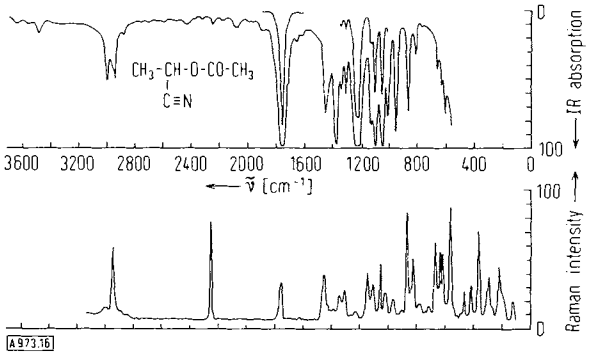


Fig. 16. Infrared and Raman spectra of (1-cyanoethyl)acetate.

The intensities of the vibration bands of X—H bonds in the Raman spectrum are often contrary to those in the infrared spectrum. The stretching vibrations of the OH groups lead to strong bands only in the infrared spectrum, whereas bands due to the vibrations of NH bonds are generally of medium intensity in both spectra. The stretching vibration of an acetylenic ≡C—H bond gives rise to a strong band in the infrared spectrum near 3300 cm^{-1}; in the Raman spectrum this band is very weak. An olefinic =C—H bond shows the stretching vibration near 3000—3100 cm^{-1} which is relatively stronger in the Raman than in the infrared spectrum. Aliphatic C—H groups show bands of medium intensity near 2800—3000 cm^{-1} in both spectra. The CH_2 and CH_3 bending vibrations also show bands of medium intensity in both spectra, near 1450 cm^{-1}. The symmetric bending vibration of the CH_3 group on carbon skeletons usually shows a band in the infrared spectrum near 1380 cm^{-1}. For saturated molecular skeletons this band is hardly detectable in the Raman spectrum; however, if the methyl group is attached to an olefinic or aromatic system a band of weak or medium intensity appears in the Raman spectrum at 1380 cm^{-1}[132]. From the intensity ratio v of this band

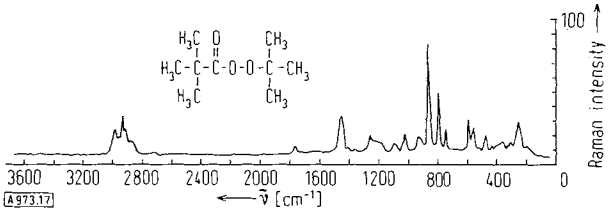


Fig. 17. Raman spectrum of liquid peroxypivalinic acid *tert*-butyl ester, 1 µl.

to that of the degenerate CH_3-bending vibration near 1440 cm^{-1} one can determine the number z of the CH_3-groups at a C=C-bond[133]: $z=1$, $v=0.26...0.56$; $z=2$, $v=0.50...0.80$; $z=3$, $v=0.82...1$ for open-chain compounds.

Some of the characteristic vibrations listed in Table 2 can usually only be found by means of the Raman spectrum; for example, the stretching vibrations of the O—O, S—S, and Se—Se groups. The O—O grouping in peroxides, peracids, and peresters gives rise to a strong Raman band in the range 700—900 cm^{-1}. Figure 17 shows this band near 868 cm^{-1} in the Raman spectrum of the *tert*-butyl ester of peroxypivalinic acid[120].

3.4. Structure Elucidation by Characteristic Band Groups

If there are n identical atomic groups in a molecule, then there are n vibrations of different frequency. All groups participate in these vibrations, but the vibrations of a particular groups are relatively independent of those of the rest of the molecule. If there are only two identical groups, one observes an "in-phase" and an "out-of-phase" vibration. The difference in the frequencies of these two vibrations is all the greater the stronger the dynamical coupling of the two groups. This coupling depends on the distance between the groups as well as on the spatial arrangement of the coupling bonds or atoms respectively. The frequencies therefore reflect the structure of configurational and conformational isomers. In the infrared and Raman spectra of isoprene (Fig. 18) the in-phase vibration ν_s of the two C=C bonds shows strong Raman bands near 1640 cm^{-1}, whereas the out-of-phase vibration ν_a gives an infrared band near 1600 cm^{-1}. All conjugated dienes in the *s-trans* conformation show $\nu_s > \nu_a$, whereas

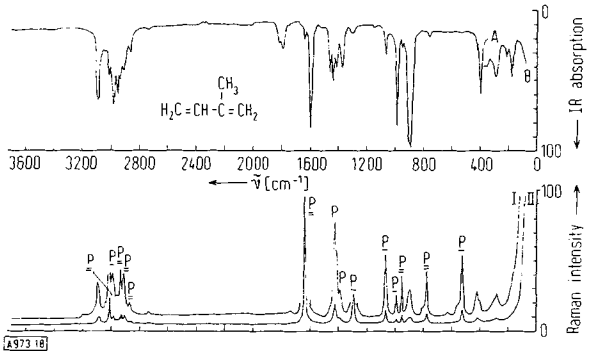


Fig. 18. Infrared and Raman spectra of liquid isoprene. IR spectrum: thickness A 20 µm, B 1000 µm; Raman spectrum: 0.3 ml, I amplification 1×, II amplification 0.2×. P: degree of depolarization $\rho=0.4...0.6$; P: 0.2...0.4; P: <0.2.

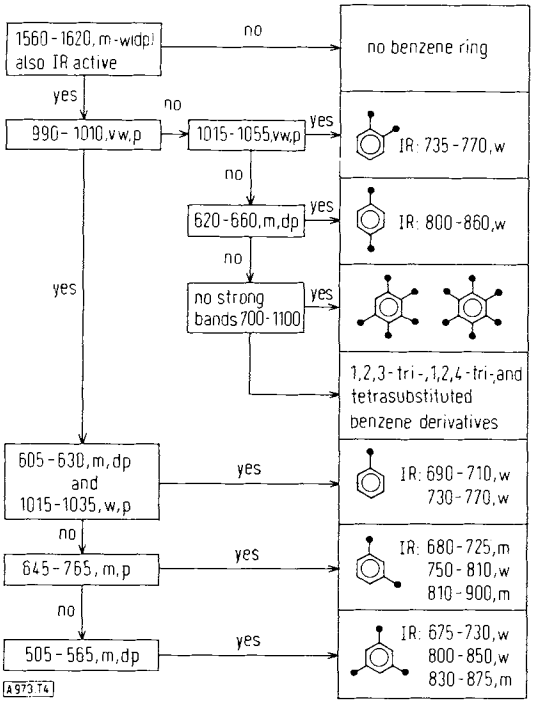
s-cis dienes show the in-phase vibration at a lower frequency than the out-of-phase-vibration, $\nu_s < \nu_a$. The position and the frequency difference of the vibrations provide information about the relative position of the two double bonds[134]. Since the vibrations which chiefly involve the single bonds between the double bonds show strong bands in the Raman spectrum, and since their frequency in the region 900 ... 1300 cm^{-1} is very sensitive to the conformation of the molecule, these can also be used for gaining information about the structure of the molecule. Characteristic groups of bands in Raman spectra have been used for elucidating the structures of several terpenes[135-138].

Until recently the band-rich Raman spectra of steroids have been accessible only with difficulty[139,140]: "The measurement of each Raman spectrum had been a miniature research problem of its own". The new techniques in Raman spectroscopy now allow the measurement of complete Raman spectra of steroids. By a systematic empirical evaluation of the frequencies and intensities, predictions about the number and the position of multiple bonds and about the *cis* and *trans* coupling of rings A and B have been made[124,125,141,142]. A scheme, similar to that shown in Table 4, has been drawn up which will facilitate such an evaluation of the relative intensities and frequencies of groups of bands in the spectra by a sequence of yes/no decisions.

The group of bands near 1450 cm^{-1} (δCH_2 and $\delta_a CH_3$) in the steroid spectra serves as a reference group: If this is the strongest band in the spectrum then presence of a saturated structure is indicated; steroids with an aromatic ring show stronger bands at lower frequencies only; if there are only bands at higher frequencies that are stronger than the reference band, isolated or conjugated double bonds at the five-membered ring D or homoannular dienes are likely. The presence of conjugated double bonds in or at the six-membered rings leads to stronger bands above and below 1450 cm^{-1}. The number and positions of these bands afford information about the nature and position of these structural elements[125]. Considerations of this kind may be generally applied also to other classes of compounds; in principle they can be used for an automatic evaluation of the spectra. The interpretation of infrared spectra by a similar scheme has been described recently[123].

It is well known that an analysis of the infrared and Raman spectra of benzene derivatives provides information about the nature of the substitution pattern and the interactions of the substituents[1,143,144]. Substituents are fingerprinted by their characteristic vibrations and by so-called "X-sensitive vibrations", the frequencies of which are strongly dependent on the mass of the substituents at the benzene system[145-152]. Here also, just one band alone is of little value—one must, as in the case of the steroid spectra, consider the existence, position and relative intensity of a group of bands. This evaluation is simplified considerably if the questions to be answered are arranged as a sequence of decisions. Table 4 shows such a scheme by which the pattern of substitution of benzene derivatives may be determined[153]. The pattern of the substituents of pyrazines also can be found from the Raman spectrum[56a].

Table 4. Scheme for the determination of the substitution pattern of benzene derivatives with the aid of characteristic bands in the Raman spectrum; intensities: m medium, s strong, vs very strong; degree of polarization: p polarized, dp depolarized. IR denotes characteristic band in the infrared spectrum [153].



A similar procedure has been used by *Willis et al.* for the identification of barbiturates by Raman spectroscopy[154].

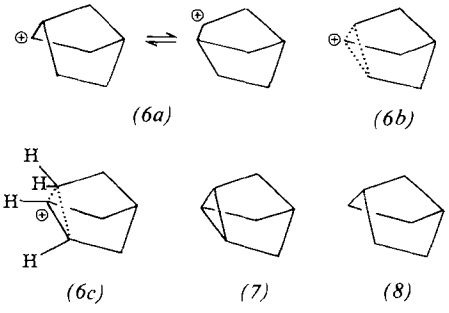
For mono-, di- and polyhalogen substituted alicycles the position and environment of the substituents may be determined by the positions and intensities of bands in the infrared and Raman spectra[155-158]. In the case of cyclic and open chain halogen substituted hydrocarbons the spectra of the possible conformational isomers can be observed and, from the temperature dependence, the free enthalpy difference may be calculated[159-165].

For some time now there has been some uncertainty about the structure of carbenium ions. By using a "super acid" as solvent *Olah et al.* were able to produce and stabilize carbenium ions, and, as a result, NMR and Raman spectra could be used in combination for the determination of structure[166,167]. They found that the *tert*-butyl cation shows practically the same vibration frequencies as trimethylboron[168,169], which is known to be planar and belongs to the point group C_{3h}. They conclude, therefore, that also the *tert*-butyl cation must be planar. A strong and polarized band appears near 347 cm^{-1} in the Raman spectrum, although—like an out-of-plane bending vibration of the skeleton—it should be Raman inactive. This finding is explained by the authors as being due to an unsymmetric arrangement of the CH_3 groups or to an association with a "gegenion" by which the symmetry is reduced from C_{3h} to C_{3v}.

The structure of the norbornyl cation *(6)* has been controversial for some time. The ^{1}H-NMR spectrum of *(6)* in "magic acid" (FSO_3H—SbF_5—SO_2) shows three signals with an intensity ratio 1:6:4, so it was impossible to make a decision between classical ions *(6a)*, which undergo

very fast Wagner-Meerwein rearrangements, and a nonclassical structure *(6b)* with delocalized σ-electrons.

Unperturbed NMR spectra of molecular species can be observed only when the life-time is larger than the duration of the spectral transition, which is in the order of $10^{-2}...10^{-4}$ seconds. In short-lived molecules, the nuclei, whose surroundings change during a reaction, only give signals of average position. In vibrational spectroscopy the duration of the spectral transition is in the order of $10^{-11}...10^{-13}$ seconds. This time is shorter than the half-life of any chemical reaction. Contrary to NMR spectra, Raman and infrared spectra should show the bands of all the components even of very fast reactions—provided that the concentration of the components is high enough.



(6a) *(6b)*

(6c) *(7)* *(8)*

Olah et al. showed that in the region of skeletal vibrations the Raman spectrum of *(6)* is very similar to that of nortricyclane *(7)*, but considerably different from that of norbornane *(8)*. These findings, as well as recent investigations of the ^{1}H- and ^{13}C-NMR spectra at low temperatures, suggest that the norbornyl cation has a nonclassical edge-protonated structure *(6c)*[170]. Further, in a similar way they recognized that 2-alkyl- and 1,2-dialkylnorbornyl cations have nonclassical structures analogous to *(6c)*, but that there are, at the same time, fast Wagner-Meerwein reactions[171,172]. It may be anticipated that Raman spectroscopy will yield important contributions to our knowledge of the structure of short-lived molecules[173].

3.5. Evaluation of Spectra with Computers and Calculation of Vibrational Spectra

In band-rich spectra of compounds of known structure, characteristic band groups may be found with the help of a computer[142]. Computers may be used for the automatic evaluation of frequencies and intensities for the elucidation of structures[123,125,153,154]. Computer programs have been developed, which use "machine intelligence" to reproduce and improve the evaluating procedures normally used by spectroscopists[174]. *Jurs et al.*[175-177] have described a procedure for the analysis of unknown substances by a weighting vector, which was developed *via* a training process in the computer. These programs are especially successful if the results of different spectroscopic procedures are combined and if, in addition, the physical laws relating to the spectra are taken into consideration. It is anticipated that Raman spectra will contribute significantly to this procedure.

The identification of unknown compounds by comparison of their spectra with the spectra of known compounds taken from spectral libraries can now be carried out rapidly by using computers[178-181]. This procedure is only meaningful, however, when the spectral libraries are large enough. Several collections of Raman spectra are already available, others are being prepared[182-186].

In view of the fact that frequencies and intensities in the Raman and infrared spectra contain more information about the properties of molecules in the electronic ground state than most other spectra, one of the most attractive chemical applications of computers is the interpretation of these spectra by calculation. Information about chemical bonds and their interactions can be obtained by comparison of simulated and observed spectra; suggested structures of unknown compounds may be confirmed or rejected. Observed vibrations may be explained, and non-observable vibrations may be calculated. Finally, from the complete set of vibrations, the thermodynamic properties of the substances may be calculated. Nowadays, the computation of vibrational frequencies is possible even for polyatomic molecules, polymers and crystals. The procedure may be briefly outlined: The potential energy of the molecule is described as a function of the change of the "inner coordinates" (bond length, bond angles, torsions) R_i in "harmonic approximation":

$$V = \tfrac{1}{2} \sum_i \sum_j f_{ij} R_i R_j \tag{20}$$

where

$$f_{ij} = \left(\frac{\partial^2 V}{\partial R_i \partial R_j} \right)_0 \tag{21}$$

are force constants, which constitude the matrix

$$\mathbf{F} = [f_{ij}] \tag{22}$$

The kinetic energy of the molecule is dependent on the velocity of change of the inner coordinates $\mathring{R}_i$:

$$T = \tfrac{1}{2} \sum_i \sum_j G_{ij}^{-1} \mathring{R}_i \mathring{R}_j \tag{23}$$

as well as the quantities G_{ij}^{-1}, which are given by the masses and the geometry of the molecule. By application of the Lagrange law of motion one obtains the secular equation[5]:

$$|\mathbf{FG} - \mathbf{E}\lambda| = 0 \tag{24}$$

whose eigenvalues λ_k yield the frequencies $\tilde{\nu}_k$:

$$\lambda_k = 4\pi^2 \tilde{\nu}_k^2 c^2 \tag{25}$$

and whose eigenvectors describe the forms of the vibrations. The frequency of a two-atomic molecule is, as is well known:

$$\tilde{\nu} = \frac{1}{2\pi c} \sqrt{f \left(\frac{1}{m_1} + \frac{1}{m_2} \right)} \tag{26}$$

where m_1 and m_2 are the atomic masses and f is the force constant.

The force constants f_{ij} describe the elastic properties and interactions of the valence electron system.

For i=j a force constant f_{ii} describes the force which is necessary for the stretching of a bond or bending of an angle. The stretching force constants are approximately proportional to the order of the bond; they are of the order 1 ... 20 mdyn/Å. The evaluation of correct interaction force constants f_{ij} with i≠j presents a difficult problem. They describe the change of elastic properties of one internal coordinate R_i when another, R_j, is stressed. A negative interaction force constant for changes in bond lengths means an increase in the bond order of R_i if R_j is stretched. Although these "off-diagonal" force constants, f_{ij}, have a value of about one tenth of the diagonal force constants f_{ii} of the matrix of the force constants [eq. (22)], their influence may not be neglected. For calculation of the vibrations of an n-atomic molecule with $z=3n-6$ normal vibrations, a maximum of $z\,(z+1)/2$ force constants is required, for example, 45 for $n=5$, 20880 for $n=50$.

Fortunately, many of the interaction force constants may be neglected because they have of very small values. For symmetric molecules several are zero by symmetry considerations and for molecules with several identical groups many of the force constants f_{ij} have the same value. Nevertheless, the number of force constants is generally larger than the number of normal vibrations. Consequently, several sets of force constants may be calculated which will reproduce *exactly* all the frequencies of a vibrational spectrum but which are *meaningless* physically. Physically "correct" sets of force constants have been established by a simultaneous evaluation of the spectra of homogolous and isotopic molecules[106,107,187–189]. The correct sets of force constants may be also sectionalized[2,3] by adjustment of the most probable distribution of the vibrational energy and by evaluation of the constants of the Coriolis-coupling and the centrifugal distortion, which may be calculated from gas spectra[190–192]. Finally, it is possible to calculate the force constants as well as the quantities which determine the intensities in the spectra $[(\partial\alpha/\partial Q)_0^2$ and $(\partial\mu/\partial Q)_0^2]$, by quantum chemical calculations: all quantities are an expression for the response of the electron system to the changed positions of the atomic nuclei[193–196].

Some years ago, in the field of inorganic chemistry complete sets of force constants for many small and symmetric molecules were derived from which the properties of the chemical bonds could be explained[106,107,197]. Calculations of the vibrations of organic and metallorganic compounds have provided a wealth of data on bonds and molecular structure[198–208].

Questions about the structure of organic compounds, for example the interactions of the bonds in conjugated compounds, may be answered by model calculations[114,115,209]. Sets of transferable force constants for organic chemical compounds have been developed by investigation of many, partly isotopically labeled molecules[187,190,210–213]. On this basis, by adjustment with observed spectra, the force constants of hexamethylbenzene, hexamethyl(Dewar benzene) *(9)*, and hexamethylprismane *(10)* have been computed and information obtained on the nature of the CC bonds[214,214a].

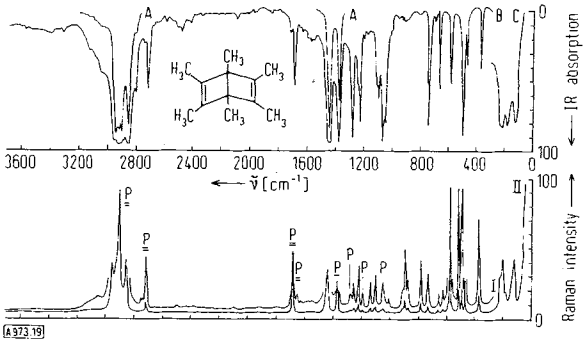
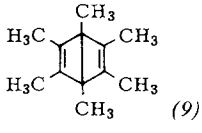
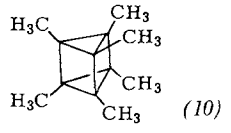


Fig. 19. IR and Raman spectra of liquid hexamethyl(Dewar benzene); IR spectrum: layer thickness A 20, B 60, C 1000 μ; Raman spectrum: I amplification 5×, II amplification 1×; degrees of polarization as in Fig. 18.

Figure 19 shows the infrared and Raman spectra of *(9)*. The calculated forms of the vibrations show that only a few vibrations are characteristic for distinct groups. The


(9)


(10)

CH_3 torsional vibrations in the region 100—250 cm^{-1} as well as the CH_3 rocking vibrations in the region 900—1100 cm^{-1} are strongly "mixed" with skeleton vibrations. Figure 20 shows some skeleton vibrations of hexamethyl-

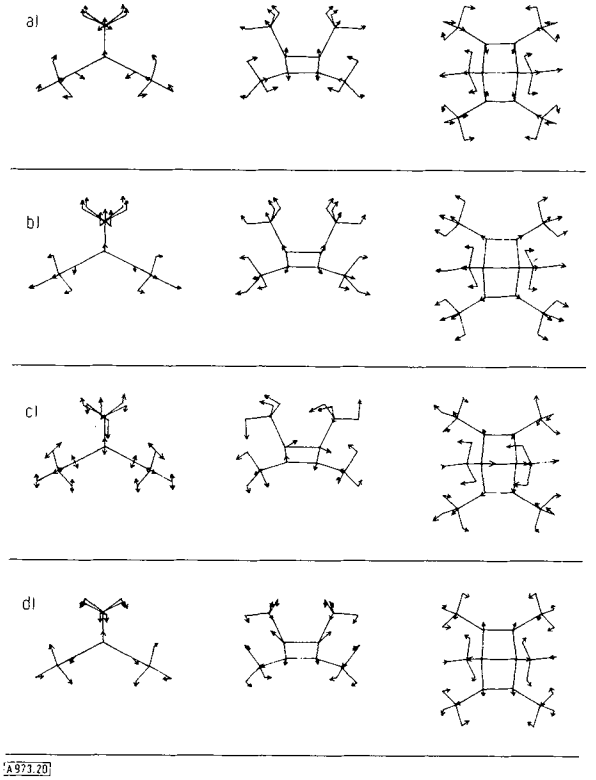


Fig. 20. Calculated amplitudes for some skeleton vibrations of the hexamethyl(Dewar benzene): 3 different views of the molecule. a) IR: 490; Raman 492, calc. 491 cm^{-1}; species A_1. b) IR: 576, Raman: 577, calc. 583 cm^{-1}; species A_1. c) IR: 659, Raman 658, calc. 657 cm^{-1}; species B_1. d) IR: 1276, Raman 1281, calc. 1274 cm^{-1}; species A_1.

(Dewar benzene), which have been drawn by a data plotter coupled with a computer. A bending vibration about the central single bond is found near 491 cm^{-1}; this band is strong in the infrared spectrum. The breathing vibration, which is the in-phase stretching vibration, appears at 583 cm^{-1} as the strongest Raman band. Also for the vibrations near 1274 cm^{-1} all CC bonds are stressed, but, in this case, in an out-of-phase mode. This band is strong in the infrared spectrum, whereas in the Raman spectrum it is very weak. A skeleton deformation vibration near 657 cm^{-1} shows very clearly a coupling of the movement of all atoms.

The in-phase and out-of-phase stretching vibrations of the C=C double bonds are found, according to calculation, to occur near 1685 or 1678 cm^{-1} respectively. Bands have been observed near 1684 (Raman) and near 1681 (infrared) cm^{-1}. Figure 21 shows the stretching force constants of the CC bonds of this molecule together with the bond lengths and bond orders which have been calculated from the force constants according to a rule given by *Siebert*[215].

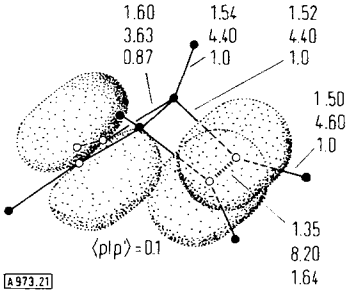


Fig. 21. Bond lengths [Å], calculated force constants [mdyn/Å], and bond orders for the CC bonds of hexamethyl(Dewar benzene).

The low bond order, 0.87, of the central single bond is not surprising, when the bond length of 1.60 Å is taken into consideration[216,217]. Moreover, the double bonds have a bond order of only 1.64; since they are of the same order as that of the double bonds in butadiene it may be concluded that mesomerism takes place. In butadiene the central bond is strengthend as a result of mesomerism (bond order 1.1), whereas in (Dewar)benzene none of the bonds in the neighborhood of the double bonds have a bond order significantly different from unity. The lower bond order of the double bond may be explained by overlap of the π-orbitals through space-homoconjugation[214a,218]. Homoconjugation in hexamethyl(Dewar benzene) is also illustrated by a splitting of the π-electron bands by 0.41 eV in the photoelectron spectrum[214a].

For hexamethylprismane *(10)*, calculation shows that the energy of the molecule, which is about 90 kcal/mol higher than that of hexamethylbenzene, is not reflected by the force constants. The bond order of the CC bonds in prismane don't deviate significantly from unity[214]. In the investigations just cited the definite assignment of calculated and observed vibrations and the adjustment of the force constants were facilitated by calculation of approximate intensities in the infrared and Raman spectra according to several different models. A coupling of the calculation of the vibrational frequencies and modes with the calculation of the dipole moments of the distorted molecule by means of the CNDO-method would seem to be promising for the evaluation of infrared intensities[214,220]. A combination of such calculations with quantum chemical calculations proves to be advantageous for many problems[219–231] and allows refinements of the results of both methods of calculation.

3.6. Raman Spectroscopy of Molecular Crystals; Intermolecular Interactions

At first sight there are only small differences between the vibrational spectra of crystalline substances and those of melts, solutions or vapors. Therefore, for many applications—for example the interpretation of the spectra by means of characteristic bands—it is of no consequence on which state of aggregation the spectra have been recorded. However, a more detailed analysis of the band positions and intensities, especially for bands at low frequencies and in the spectra of single crystals using polarized radiation, provides a wealth of information about the molecules, their interactions and their arrangement in the crystal.

In the crystal the molecule is situated on lattice sites, which are determined by the equilibrium between attractive and repulsive forces. The incorporation of a free molecule into a crystal lattice has important consequences:

1. Free rotation of molecular groups is hindered: usually the molecules are incorporated into the lattice only in one distinct conformation. The symmetry of the site is often lower than that of the isolated molecules, so vibrations, which—for the free molecule—belong to "forbidden" species, may become active and degenerate vibration levels may split. Finally, the static forces in the lattice may change the molecular force field and therefore may produce a shift of band frequencies (Figs. 22a and

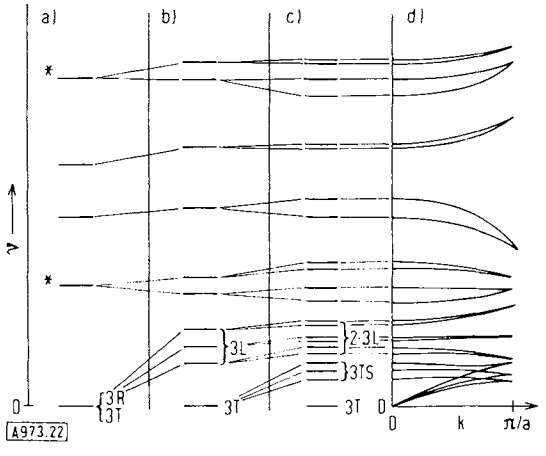


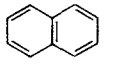
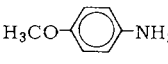
Fig. 22. Variation of the frequencies by the incorporation of a tetraatomic molecule with two degenerate vibrational states (*) in a crystal lattice; a) spectrum of the free molecule, R = rotations, T = translations; b) static influence of the crystal lattice. The degenerate states split, the free rotations change into librations L; c) dynamic coupling of the vibrations of molecules within a primitive unit cell with $z = 2$ molecules. Each vibrational level of a molecule splits into z components and $3z-3$ translational vibrations TS and $3z$ librations L appear; d) dependence of the vibrational frequencies on the wave vector k of the coupled vibrations of all unit cells in the lattice. The three "acoustic branches" arise from the three free translations with $\tilde{\nu} = 0$ and $k = 0$ of the unit cell; all vibrations of the unit cells with $\tilde{\nu} = 0$ and $k = 0$ are "optical branches".

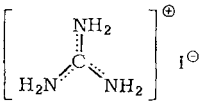
22b). In spite of these influences the spectra may be interpreted to a first approximation by the "oriented-gas-model". From the intensities of the bands in the spectra of a single crystal, the angle between the molecular and the crystal axes may be calculated and the vibrations may be assigned to the vibrational species of the molecule[231-234].

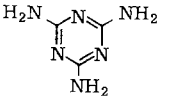
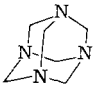
2. In addition to the static lattice forces dynamic interactions of the vibrating molecules are also shown by the spectra. The primitive unit cell (which may be a fraction of the crystallographic unit cell) is the dynamical unit of the lattice, the symmetry properties of which determine the selection rules. The vibrational terms of the molecules split into as many components as there are molecules in the primitive cell. For these vibrations all molecules in the cell are moving similarly, but with different relative phase. The three free rotations and the three translations of each molecule are "frozen" in the lattice; instead of these, one observes for z molecules in the unit cell $3z$ librations (torsional vibrations) and $3z-3$ translational vibrations (Fig. 22c). These vibrations are called "external vibrations" or lattice vibrations.

3. Finally, the vibrations of neighboring primitive cells also couple. A lattice consisting of N primitive cells contains in fact N times as many different vibrational states as one primitive cell. They differ in the phase difference ($\varphi = 0 \ldots \pi$) of the same vibrations in different primitive cells. For the characterization of these vibrations one uses the "wave vector" $k = \varphi/a$, where a is the lattice constant. The frequencies of the "inner" vibrations, librations, and translational vibrations of the primitive cell constitute, when plotted as a function of k, the so-called optical branches. The (for $k = 0$) free translations of the primitive cell constitute the so-called acoustic branches (Fig. 22d). This name indicates that this branch describes those elastic vibrations which form the basis of the Debye theory of specific heat.

The sum of all vibrational states is reflected by the "inelastic neutron spectra" and by thermodynamic properties of the crystal. The wave lengths of the radiation, by which the Raman spectra are excited and the infrared are observed, are 1000 to 10000 times as large as the lengths of the axes of the primitive cell. Therefore one observes in the spectra only those vibrational states of the crystals for which neighboring primitive cells are vibrating almost in-phase, that is with $k \sim 0$. Hence, for the interpretation of the vibrational spectra it is sufficient to analyze all vibrations of *one* primitive cell.

(11)   *(12)*

 *(13)*

(14)   *(15)*

The theory of the vibrational spectra of crystals is based on the work of several authors[235-245]; some new monographs and reviews on this subject have been published recently[246-248a, 265c]. In the Raman spectra of molecular crystals the strongest expression of the crystal forces are the lattice vibrations—the librations and translational vibrations, usually occurring in the region 10—200 cm^{-1} (Fig. 23). The number, frequency, and width of the observed bands depend on the shape of the molecules, the symmetry of the lattice sites, and the interactions of the molecules in the lattice.

Figure 23 shows typical spectra of lattice vibrations taken from an investigation of the lattice vibrations of numerous molecular crystals[249]. For molecules having centers of symmetry there are only librations active in the Raman spectra. In the case of naphthalene there are two centrosymmetric molecules in the primitive cell, so one finds 6 librations, in-phase and out-of-phase vibrations of both molecules about the axes of inertia (Fig. 23a). The intensity

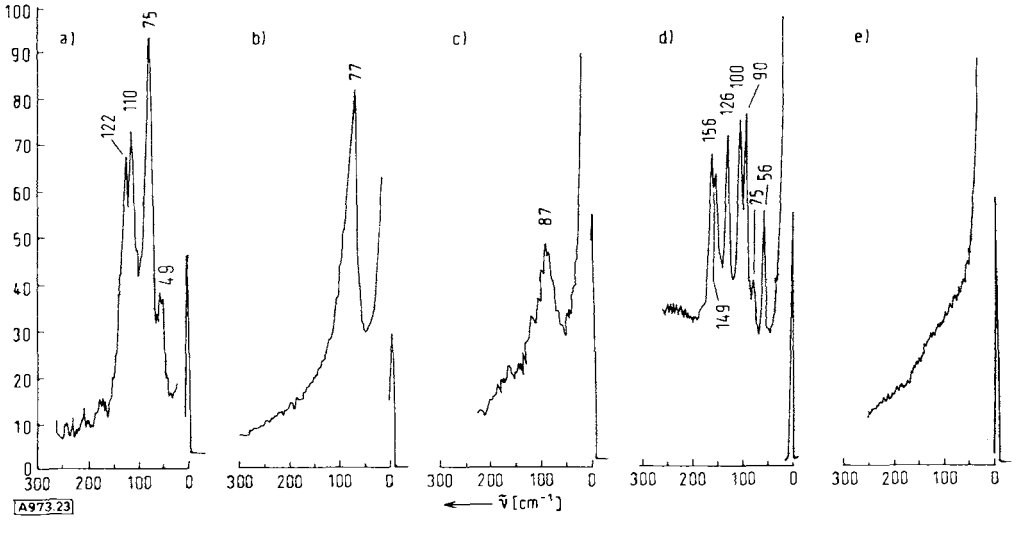


Fig. 23. Range of the librations and translational vibrations in the Raman spectra of some crystal powders: a) naphthalene *(11)*, b) *p*-aminoanisole *(12)*, c) guanidinium iodide *(13)*, d) melamine, *(14)*, e) urotropine *(15)*. The spectra were recorded using the exciting line 4358 Å of a Hg low-pressure arc [249].

of the librations in the Raman spectrum is larger, the larger the differences of the main polarizabilities of the molecules[235, 236, 241]. As a consequence the Raman spectra of hexamethylenetetramine, a molecule with cubic symmetry, shows no librations. In guanidinium iodide *(13)* (Fig. 23c) and melamine *(14)* (Fig. 23d) the polarizability in the direction of the threefold axis is significantly smaller than that in the molecular plane. Similarly, in *p*-aminoanisole *(12)* (Fig. 23b) one of the polarizabilities, in the direction of the substituents, is significantly larger than the polarizabilities perpendicular to this axis. In the case of these three compounds, therefore, one should expect only two librations of the molecule to modulate the polarizability of the crystal and thus to give rise to bands in the Raman spectrum. Their frequencies may coincide if the moments of inertia and significant intermolecular force constants for both vibrations are equal. It can be seen from Figure 23d that melamine shows at least seven bands. Here, significant force constants for the different librations about axes in the molecular plane are different, and, in addition, translational vibrations are also active[249, 250].

Predictions as to the number and the properties of the vibrations of the primitive cell may be made with the aid of factor group analysis[246–248a]. The magnitudes of the intermolecular and intramolecular force constants may be determined by calculation of the vibrations. If possible, the spectra of the single crystals are used as a basis.

As Figure 24 shows, in the case of the imidazole single crystal different Raman spectra are obtained for each of the six different components ($\alpha_{ij} = \alpha_{ji}$, i, j = x, y, z) of the polarizability tensor of the crystal[251, 252]. Imidazole crystallizes monoclinically (C_{2h}^5) with four molecules in the primitive cell, where the two pairs are parts of chains which line up the molecules in the z-direction by hydrogen bonds.

As a consequence of the intermolecular N ... H—N hydrogen bonds the frequency of the NH-stretching vibration is reduced from about 3200 to 2800 cm^{-1}; due to Fermi resonance with overtones and combinations of skeleton vibrations near 1200 ... 1500 cm^{-1}[252, 253] there is a band of peaks[254] instead of just one peak. As expected, this band shows up strongest in the spectrum of the tensor component α_{zz} of the crystal. Since the molecular planes are tilted only slightly from the yz plane of the crystal, the planar skeleton vibrations and the CH stretching vibrations show up strongest in the spectra of the components α_{zz}, α_{yy} and α_{yz}. In the calculation of the vibrations of crystalline imidazole[252], and of other molecular crystals[255–258], it has been shown that the intermolecular force constants also influence the frequencies of the inner vibrations. In the calculation of external force constants one gets values that are too small if one assumes that the molecules are rigid.

External force constants for the elastic forces between non-bonded atoms may be also calculated by using the second derivatives ($\partial^2 V/\partial r^2$) of potential functions which have been established by other methods. One may use atom-atom potential functions of the *Lennard-Jones* or *Buckingham* type[259], such as for example, those according to *Warshel* and *Lifson*[260] or *Kitaigorodski*[261]. *Shimanouchi* has shown that the force constants depend mainly on the repulsive term in the potential functions[255, 262].

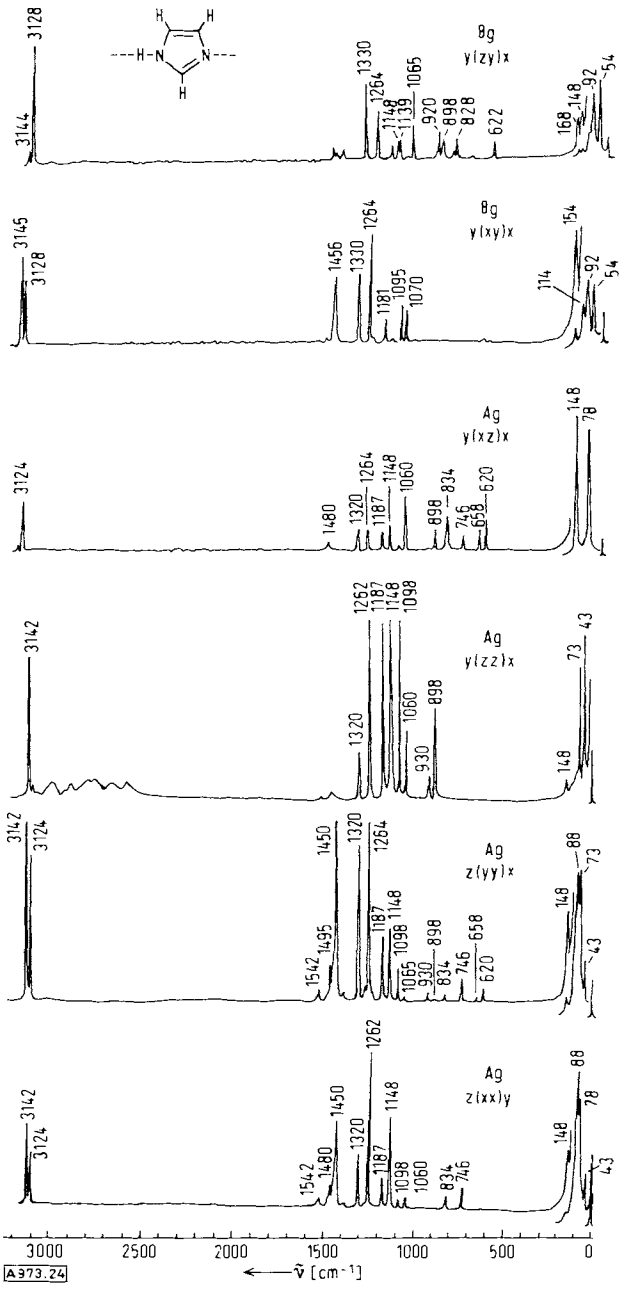


Fig. 24. Raman spectrum of an imidazole single crystal; y(zy)x means: illumination parallel to the crystal axis y, electric vector of the exciting radiation parallel to z, electric vector of the Raman radiation parallel to y, and direction of observation x. The librations and the translational vibrations are in the range 20 —200 cm^{-1}. The vibrations of the N—H bonds appear in the spectrum Ag, y(zz)x in the region about 2700 cm^{-1} together with some Fermi resonance bands (cf. also Table 5).

In Figure 25 the force constants for intermolecular H ... H, C ... H, O ... H and S ... H-bonds are given which have been found by calculation of the vibrations of crystalline benzene, naphthalene[255], thiourea[257, 263], and benzoic acid[264, 265]. From Figure 25, it can be seen that the stretching force constants of inner vibrations are in the region of 2 ... 20 mdyn/Å. Most of the intermolecular force constants are of the order of 0.001 ... 0.1 mdyn/Å. Stretching force constants in the region 0.1 ... 1 mdyn/Å are either related to forces between non-bonded atoms in the same molecule or indicate hydrogen bonds. We have been able

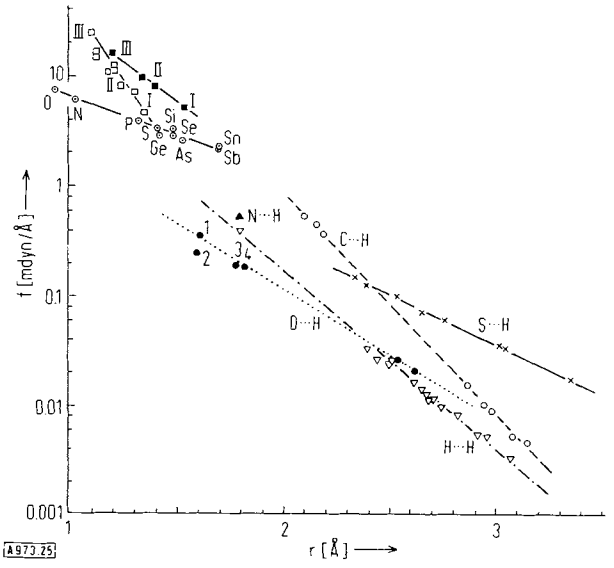


Fig. 25. Intramolecular and intermolecular stretching force constants of different bonds as a function of their bond lengths. I, II, III single, double, and triple bonds, ▪ CC and □ NO [197], ⊙ hydrides [106], ▽ H ... H [255], × S ... H [257, 263], ● O ... H (examples: 1 benzoic acid, 2 formic acid, 3 water, 4 uracil) [264, 265], ○ C...H, ▲ N...H (example imidazole).

(– – –) 6500 $e^{-4.57\,r(C\ldots H)}$
(– · – · –) 163 $e^{-3.534\,r(H\ldots H)}$
(· · · · ·) 33 $e^{-2.82\,r(O\ldots H)}$
(— —) 16.5 $e^{-1.03\,r(S\ldots H)}$

talline thiourea[256, 257, 263]. The frequencies of all lattice vibrations, including those with $k \neq 0$ (Fig. 22), have been calculated for a number of different small molecules in the crystalline state[265a]. Recently a method for calculation of the vibration of glass-like molecular networks has been developed and applied to As_2Se_3 and As_2S_3[265b]. The interpretation and calculation of the vibrational spectra of inorganic solids has been discussed by *Becher*[265c].

The intensities of the vibrations, especially those of the lattice vibrations in crystals, make it possible to draw conclusions about the interactions of neighboring molecules in the lattice. During translational vibrations the molecular polarizability ellipsoid is shifted parallel; so, as was previously assumed, there may be no change in the polarizability of the crystal for these vibrations. Actually, translational vibrations often lead to very strong bands such as, for example, the bands near 43 and 73 cm^{-1} in the spectrum of imidazole (Fig. 24, Table 5). The intensity of the librations in the Raman spectrum may be calculated from the molecular polarizabilities using a model developed by *Kastler* and *Rousset*[235,236]. Here also, the measurements of absolute intensities[266] show that the observed intensities are very much greater than the calculated intensities. For thiourea the intensity of the libration at 119 cm^{-1} (species A_g) has been calculated to be 0.40, whereas the observed value was 2.26 ($\cdot 10^{-28}$ cm^2/molecule)[266]. These discrepancies may not be explained by a coupling with other vibrations or by a dipole or quadrupole interaction[267,268], for these effects would be too small. They show rather the intermolecular perturbation of the electronic system of neighboring molecules in the crystal. Crystal orbitals are formed from molecular orbitals by intermolecular bonding and antibonding interactions. As a result of the modulation of the intermolecular distances in lattice vibrations the intermolecular overlap-integrals are also modulated and, consequently, also the energy levels of the crystal orbitals, the polarizabilities, and the dipole moments. This perturbation can therefore also be observed from the intensities of the bands in the far-infrared spectra and can be determined by quantum mechanical calculations[269].

Table 5. Calculation of the lattice vibrations of imidazole. Assignment of the librations L and translational vibrations T of the species Ag to the observed bands. Calculated frequencies and potential energy distributions for the force constants (see also Fig. 24).

Vibration	Frequency $\tilde{\nu}$ [cm^{-1}] obs.	calc.	Distribution of the potential energy of the vibrations
L_z	148	134	63% H...H
T_x	88	108	50% N...H—N
L_x	78	76	44% H...H + 22% C...H
T_y	73	69	38% H...H + 26% C...H + 16% N...H—C
T_z	43	25	45% N...H—C + 42% C...H

The Raman spectrum also provides information about the mechanism of the change of crystal modifications, *e.g.* about the Λ-point of hexamethylbenzene[214,270] or about the transformation into the ferroelectric state in thiourea[256,257,263]. In many investigations information about the properties and structures of crystalline complexes have been derived. Examples are: complexes with xenon difluoride[271], complexes and inclusion compounds of urea and thiourea[48,234,272], and charge-transfer complexes[273–276].

Investigations on the temperature dependence of the line widths and on the change of frequencies and intensities during phase transitions yield information about intermolecular interactions, and about the structures of liquids[277–280], for example, in the crystalline, glass-like, and liquid states of glycerine[281–282] and other compounds containing hydrogen bonds[283]. From the temperature dependence of the line widths and line shapes of the librations the times of reorientation and characteristics of the anharmonicity of the lattice potentials may be calculated[283a].

3.7. Raman Spectroscopy of Synthetic Polymers

Macromolecular compounds often contain both crystalline and amorphous structural elements. Raman spectroscopy makes it possible—as was described in Section 3.6—to obtain data on the properties of crystalline structures. In addition to this the spectra reveal characteristic properties of the molecules and of parts of the molecules. Consequently, there are numerous applications in the field of macromolecular compounds: from the frequency of the total symmetric bending vibration of chain molecules (accordion vibration, δ_s(CC) in Table 1) in the region 10 ... 200 cm^{-1} conclusions can be drawn about the length of the chains or the length of the straight parts of folded macromolecules[1,284]. Decisions about the structures of the crystalline region[285,286] have been made possible and data has been obtained on crystallinity[287–290], tacticity[291–293], interactions at the interfaces in glass-fiber reinforced polymers[294], the structure of polarizing foils[295] and cross-linked polyesters[296], the kinetics of to show that there are S ... H—N hydrogen bonds in crys-

polymerization[297] and vulcanization[298] and finally, the conformation of dissolved polymethacrylic acids[299]—these examples serve to illustrate the scope of applications in the field of macromolecular compounds. Here also, model calculations lead to the most definite results, so the large expense incurred is often worth while[300-302]. Unfortunately, the applicability of Raman spectroscopy to the field of macromolecular compounds is limited by fluorescent impurities. Often they cannot be removed and therefore may render the recording of a Raman spectrum of a polymeric substance impossible. This is also true in the case of the biopolymers discussed in the next paragraph.

3.8. Raman Spectroscopy and Problems in Biochemistry

Raman spectroscopy is a suitable method for use in investigating biochemical problems, largely because the study of molecules in their normal environment—aqueous solutions of low concentration—is possible. This is not so in the case of infrared spectra because of the strong absorption bands of water. Moreover, in the case of Raman spectroscopy the amount of sample required may be as little as 1 mg or less[303]. Although the investigations are often beset with difficulties because of the low intensity of the Raman bands and possible interference by fluorescence spectra, a number of most interesting applications to biomolecules have been made in recent times. In many cases the fact that the intensity of the Raman lines is enhanced when the exciting line is shifted into the neighborhood of the absorption bands of the compounds (resonance Raman effect) has been used. Utilizing this effect, *Rimai, Gill et al.* have been able to record the Raman spectra of samples of carrots and tomatoes. These spectra are almost identical with those of carrot juice and tomato juice and of solutions of β-carotin and lycopène in *n*-hexane[304]. The Raman spectra of some stereoisomeric vitamin A derivatives were also recorded and bands in the region 1100—1400 cm^{-1} have been shown to be characteristic for the different isomers[305].

The same workers also showed that by a systematic shift of the exciting line, excitation profiles for the Raman spectra of carotinoids could be derived which permitted recognition of electronic states (triplet states) that were otherwise accessible only with difficulty[306, 307].

Intact bovine retinas gave a Raman spectrum that is similar to the spectrum of retinylidenehexylamine in acid solution[308]. The spectra of 11-*cis* retinal, of other stereoisomers, and of Schiffs bases of the visual pigments, which have been models for the study of the visual process[309, 310], have been recorded. Resonance Raman spectra of metalloporphyrins[311] and haemoglobins[312] have also been recorded and information on the structure of the chromophore has been obtained. Some publications describe the investigation of the nature of the bonds of the iron atom in iron proteins, *e.g.* enzymes of the respiratory chain[313-315].

The Raman spectra of carbohydrates are more characteristic of the skeleton than are the infrared spectra; some recent investigations deal *inter alia* with the monosaccharides, with the disaccharides maltose and cellobiose[316], and with the conformation of the side-chains in celluloses of cell walls[317]. Perturbations of the structure of micelles in liquid dipalmitoyllecithine layers by cholesterin[318, 319] have been studied by observing the changes of bands in the region 1100 cm^{-1}. Raman spectroscopy should be a suitable method for the analysis of membranes *in situ*[320]. The application of Raman spectroscopy to the analysis of terpenes and steroids has already been discussed[124, 125, 135-138, 141, 142].

In the Raman spectra of proteins, as *Lord et al.* have shown for the spectra of ribonuclease, α-chymotrypsin, and lysozyme[321-323] the different amino acids can be recognized by the vibrations of their side chains. These are dependent on the conformation of the peptide bonds. The ν(SS) and ν(CS) near 500 and 700 cm^{-1} of different proteins occur at different positions and with different intensities. This allows conclusions to be drawn about the number and conformation of the SS bonds. Finally, the structure of the chain may be deduced from the frequency of the Raman bands of the amide groups. In the series α-helix, coil, β-arrangement (pleated sheet), for example, the frequency of the amide III band (in-phase vibration of the CO and CN bonds) is decreased from 1266 through 1248—1232 cm^{-1} in the spectra of glucagon[324]; in the region of the amide I band (namely the CO stretching vibration) near 1630—1700 cm^{-1}, on the other hand, the frequency is raised from 1660 through 1665—1674 cm^{-1}. The spectra of human serum-albumin have been analyzed[325] and deductions have been made about the structure of natural and denaturated insulin and various denaturation processes in lysozyme[326-329].

Several chain vibrations at low frequencies reveal the conformations of the peptide chains[330]. Further investigations describe the interactions between proteins and ligands[331] as well as the consequences of tissue calcification[332].

Harada and *Lord* have investigated the Raman spectra of the complex of 1-methylthymine with 9-methyladenine and of some crystalline bases of the nucleic acids. By way of frequency calculations they have been able to locate the hydrogen bond vibrations as weak Raman bands in the region 70 ... 125 cm^{-1}; also strong librations and translational vibrations occur below 100 cm^{-1}[333]. *Tsuboi et al.*[334] used the bands due to the different bases in the Raman spectra of formylmethionine transfer-RNA from *E. Coli* for a quantitative analysis[334]. *Peticolas et al.* examined the various implications of chain conformation upon the spectra of DNA and RNA[335, 336]: the total symmetric ring stretching vibrations of the bases show lower intensity when the rings are stacked side by side. Bands near 800 cm^{-1}, attributed to the symmetric stretching vibration ν_s(O—P—O) of the polyester backbone, are especially sharp and intense for the double helix structure of the nucleic acids. Finally, in the region of the C=O and the C=C double bond vibrations, bands are to be found which are sensitively dependent on the arrangement of the bases. With the aid of these bands the structures of and denaturating processes in natural nucleic acids—soluble and transfer-RNA from yeast and calf thymus-DNA—could be elucidated[335-338].

3.9. Conclusion

In this paper only a small part of the old and new chemical applications of Raman spectroscopy have been considered. In our selection of material we have naturally referred to results from our own field of work, and work in other fields, for example, inorganic chemistry, may have been somewhat neglected.

Applications to problems of solid state physics have scarcely been touched upon, while the large field of "non-linear" effects (for example the hyper-Raman-effect[339]) have not even been mentioned. The inelastic scattering of electromagnetic radiation by inner electrons or by nuclei, both of which have also been called "Raman effects" (X-ray-Raman-effect[340, 341], nuclear Raman effect[342]) still don't offer any interesting applications in chemistry. There will possibly be some analytical applications of the resonance Raman effect, which, at the moment, is of interest mainly for theoretical investigations[24, 343].

Techniques which use the Raman effect for the investigation of "extremely fast" reactions (in the range $10^{-7} \ldots 10^{-12}$ sec) will help to solve a number of chemical problems[344, 345]. The combined use of data from Raman and photoelectron spectroscopy has only just begun[214a, 346]. The application of circular polarized exciting radiation for the measurement of an effect similar to circular dichroism, the "Raman circular intensity difference" has been investigated theoretically[347, 348] and may, in the future, contribute significantly to the elucidation of the structures of chiral molecules[349]. Data complementary to those of UV or infrared rotational dispersion[350] are anticipated; here, there is also a Faraday effect variant[351].

Whether a Raman-radar technique for the determination of air contaminants fulfils expectations[84–89] remains open: nevertheless, the experiments in this field yield important data on scatter cross sections[352] and molecular constants and are providing new methods for the measurement of temperatures and concentrations in gases[353, 354]. The determination of contaminants in water by means of Raman spectroscopy would seem not to be unrealistic[355]. Several developments may be expected regarding apparatus: improvement of the sample arrangement and light power of the instruments, construction of inexpensive routine instruments, and perfection of tunable laser light-sources.

The apparently universal application of Raman spectroscopy in the temperature range from 1 to 2000 °K for amounts of substance in the nanogram region, for highly diluted solutions, for air sensitive, explosive and colored substances tends to conceal the limitations and difficulties of the method. Sometimes Raman spectra can be recorded only after great effort has been put into the preparation and purification of the sample. Many samples referred to as being "analytically pure" show strong fluorescence due to products of decomposition or traces of stop cock grease which may mask the Raman spectrum completely. Procedures have been developed for the preparation of samples especially for Raman spectroscopy[18]. In the case of polymers the purification is sometimes very difficult, if not impossible. Compounds which absorb over the whole visible region often give no Raman spectrum at all. Photochemical reactions during the excitation of Raman spectra sometimes lead to fluorescent impurities being transformed into non-fluorescent compounds; in a few cases the reverse process is observed. Substances which contain mechanical impurities like dust may decompose by the heat created by absorption of the laser beam. Liquids of low boiling point sometimes boil in the region of the focus of the laser beam, while biological samples may denaturate. The successful application of Raman spectroscopy is only possible if the limits of the method are taken into account and if it is recognized beforehand that preparation of the sample is often more difficult than the actual recording of the spectrum. Careful preparation of the samples is therefore just as important as the procurement of reliable spectrometers and light sources.

Today Raman spectroscopy can be applied to the study of most problems where this technique is known, in principle, to be suited. There are some investigations in which Raman or infrared spectra can yield equally informative data. Since Raman spectroscopy is more sensitive toward interferences (for example by absorbing of fluorescing impurities) and since infrared spectroscopy and infrared spectrometers are more commonplace, the solution of such problems will generally be accomplished by infrared spectroscopy. It has been estimated that about only 5 to 10% of the problems encountered in a normal infrared spectroscopy laboratory in industry are best solved by Raman spectroscopy. Only in the case of problems where a complete knowledge of vibrational spectra is necessary does one have to combine the use of Raman and infrared spectroscopy; for example, in the determination of the symmetry of molecules, in the calculation of spectra or force constants, and in the determination of thermodynamic properties. On the other hand, it has been shown that Raman spectroscopy is more suitable than infrared spectroscopy for a number of analytical problems.

It is to be expected that Raman spectrometers will find a future in large laboratories of the chemical industry, in many research institutes, and in most chemical departments of universities. Raman spectroscopy should prove to be an important instrument in the orchestra of modern physical methods in chemistry.

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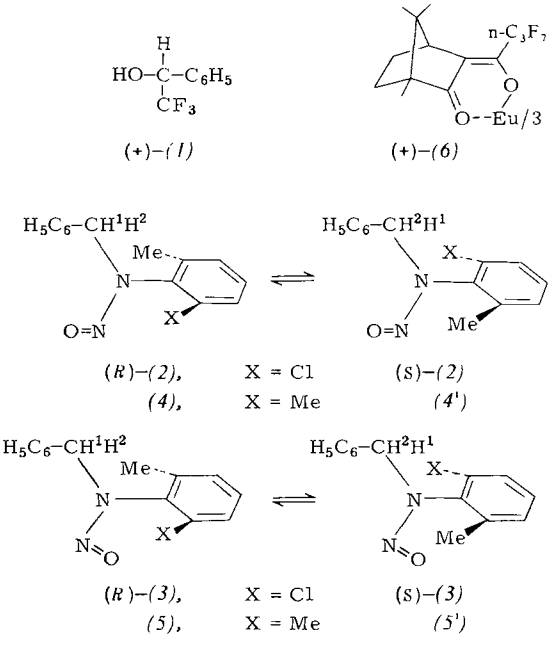
Determination of Rate of Internal Rotation by ^{1}H-NMR Spectroscopy in the Presence of Optically Active Auxiliary Compounds[**]

By *Albrecht Mannschreck*, *Violet Jonas*, and *Bernd Kolb*[*]

Different NMR spectra can be observed for enantiomers which undergo a sufficiently strong interaction with an optically active auxiliary compound[2, 3]. For example, addition of 2,2,2-trifluoro-1-phenylethanol (+)-*(1)* causes most of the ^{1}H-NMR signals of racemic nitrosoamine *(2)*[4] to split at 10 °C[1]. *(R)*-*(2)* and *(S)*-*(2)* interconvert through a half rotation about the *N*-aryl bond[5], so that a kinetically induced coalescence of the signals of matching protons in each diastereomeric association complex is possible[1]. We are now for the first time reporting this type



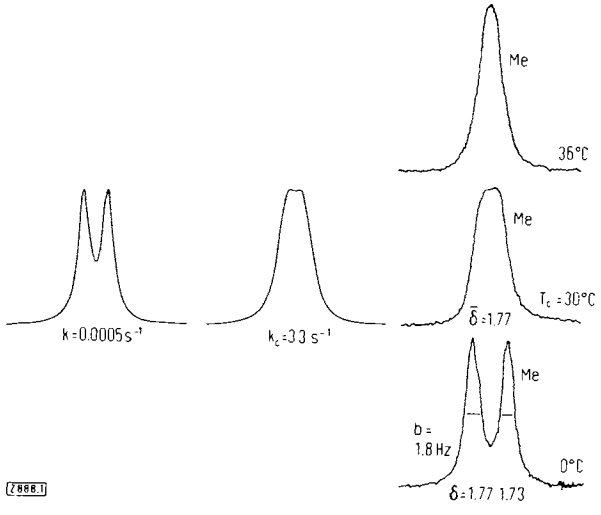


Fig. 1. ^{1}H-NMR signals (100 MHz) of the methyl groups of (*E*)-(2,6-dimethylphenyl)-benzylnitrosoamine *(4)* in CCl_4 in the presence of (*S*)-2,2,2-trifluoro-2-phenylethanol, (+)-*(1)*, as auxiliary compound; see Table 1. *b*: Width at half height of both methyl signals. For the spectrum at 30 °C (right), two simulations [9] with different *k*-values for half-rotation about the *N*-aryl bond are shown: $k = 3.3\,s^{-1}$ (middle, fitting) and $k = 0.0005\,s^{-1}$ (left, non-fitting). For both simulations $\Delta\delta = 0.024$ and $b = 1.4$ Hz [9] were used.

Table 1. ^{1}H-NMR data for nitrosoamines *(2)* and *(4)* in the presence of the optically active auxiliary compounds (+)-(1) and (+)-*(6)*.

	Auxiliary cpd. solvent [a]	*T* [°C]	δ(CH_2) [b] δ(CH_2).	δ(Me) [b] Δδ(Me)	T_c [°C]	$\Delta G_c^{\neq}$ [kcal/mol]
(R)-*(2)*⇌*(S)*-*(2)*	(+)-*(1)* CCl_4	10	H^1: 5.64 *0.014*	H^2: 4.31 *0.0*	1.57 *0.022*	26	17.1
	(+)-*(6)* $CCl_4/CFCl_3$ (11:5)	1	H^1: 9.57 *0.26*	H^2: 6.48 *0.16*	2.77 *0.137*	32	16.5
(4)⇌*(4')*	(+)-*(1)* CCl_4	0	4.88 *0.0*		1.75 *0.036*	30	17.0
	(+)-*(6)* CCl_4	1	8.76 *≈0.1*		3.17 *0.185*	39	16.7

Δδ: Chemical shift difference *(italicized numbers)* of the two signals which arise in the presence of the auxiliary compound.
T_c: Coalescence temperature of the methyl resonances. Oscillator frequency: 100 MHz when (+)-*(1)* was used, 60 MHz when (+)-*(6)* was used.
[a] Concentrations [4]:
6.3 mol-% sum *(2)*/*(3)* and 37.5 mol-% (+)-*(1)*;
2.56 mol-% sum *(2)*/*(3)* and 0.71 mol-% (+)-*(6)*;
3.0 mol-% sum *(4)*/*(5)* and 21.2 mol-% (+)-*(1)*;
2.88 mol-% sum *(4)*/*(5)* and 0.86 mol-% (+)-*(6)*.
[b] In cases where two signals arise in the presence of the auxiliary compound, the average of their shifts is given.

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of coalescence and a new method, based upon this phenomenon, of determining the rates of intramolecular processes in molecules capable of association.

Compound *(2)* seemed to us to be especially suitable for the first experiments with this objective because here

the *N*-aryl rotation takes place at a favorable rate for NMR line-broadening measurements[5]. However, we also introduced the *achiral (4)* into the investigation. In unassociated *(4)* it is *not* possible to follow the rotation by NMR spectroscopy, because the shifts of the methylene protons H^1 and H^2 must be identical, this also being true for both methyl groups. However, *(4)* should form an "*enantiomeric* association complex" with an optically active auxiliary compound, with the result that H^1 and H^2, as well as both methyl groups, become diastereotopic to each other, thus potentially leading to different δ-values in each case[6].

In fact, after the addition of (+)-*(1)*[8], *(4)*[4,7] displays two methyl signals at 0 °C (Table 1), which coalesce upon raising the temperature (Fig. 1, right). We could simulate[9] the line shape at $T_c = 30$ °C assuming that a fast *N*-aryl rotation corresponding to *(4)* ⇌ *(4')* takes place with a rate constant $k_c = 3.3\,s^{-1}$ ($\Delta G_c^{\neq} = 17.0$ kcal/mol) (Fig. 1, middle). Use of an arbitrary but very small *k*-value led to an incorrect curve (Fig. 1, left). Thus, the observed coalescence of the methyl signals is not a consequence of the likewise detected decrease of their chemical shift difference Δδ with increasing temperature; rather, a coalescence which is brought about *kinetically* is involved. This conclusion is substantiated by the use of (+)-*(6)*[8] as the auxiliary compound; here Δδ corresponding to the two methyl resonances of *(4)* is of such a size that their broadening, coalescence, and sharpening upon raising the temperature is already clearly recognizable without simulation (Fig. 2). The resultant $\Delta G_c^{\neq}$ value of 16.7 kcal/mol at 39 °C is similar to that obtained upon addition of (+)-*(1)*. Analogous results (Table 1) were obtained for chiral *(2)*[4], which in contrast to *(4)* forms diastereomeric association complexes[11].

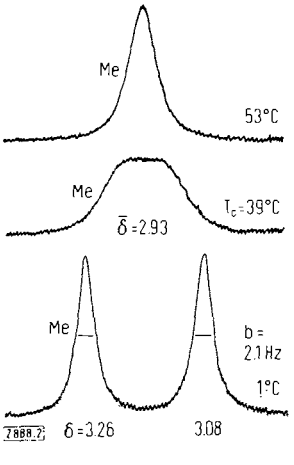

Fig. 2. ^{1}H-NMR signals (60 MHz) of the methyl groups of (*E*)-(2,6-dimethylphenyl)-benzylnitrosoamine *(4)* in CCl_4 in the presence of tris[3-(heptafluoropropylhydroxymethylene)-D-camphorato]europium(III), (+)-*(6)*, as auxiliary compound; see Table 1. *b*: width at half height of both methyl signals.

Beginning with the not quite certain assumption of 1:1 association complex formation between *(4)* and the auxiliary compound (+)-H, one obtains for this case the following kinetic scheme:

$$\begin{array}{ccc} (4) + (+)\text{-H} & \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} & (4)\cdots\cdots(+)\text{-H} \\ k_f \uparrow\downarrow k_f & & k_a \uparrow\downarrow k_a \\ (4') + (+)\text{-H} & \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} & (4')\cdots\cdots(+)\text{-H} \end{array}$$

The association complex formation (k_1) and its dissociation (k_{-1}) are generally considered to be fast in comparison to rotation in the association complex (k_a) or in the free nitrosoamine (k_f). The question whether k_a or k_f correspond to the measured *k*-value must at present remain open. However, the kinetic results for *(2)* in CCl_4 and in $CCl_4/CFCl_3$ at 26 and 32 °C[10], respectively (Table 1) are similar to the barrier of 16.5 kcal/mol obtained in the absence of an auxiliary compound in C_4Cl_6 at 70 °C using the coalescence of the signals of H^1 and H^2[5]. The exact experimental comparison of all activation parameters under consistent conditions, as well as the measurement of $\Delta G^{\neq}$ at different concentrations of (+)-*(6)* will help to clarify the problem further.

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[4] Because of the partial N—N double bond, in addition to the (*E*) isomer *(2)*, the (*Z*) isomer *(3)* coexists in solution, for which diastereomeric association complexes were also detected [1]. That the barrier to *N*-aryl rotation in *(3)* is greater than 20 kcal/mol [5], is confirmed by investigation of the association complex up to 100 °C. The hitherto unknown barrier to *N*-aryl rotation was found to be $\Delta G_c^{\neq} = 24$ kcal/mol at *ca.* 160 °C for *(5)* in C_4Cl_6 in the presence of (+)-*(6)*.

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[8] (+)-*(1)*: $[\alpha]_D^{23} = +31.40$ (neat); (+)-*(6)*: $[\alpha]_D^{23} = +151$ ($c = 1.27$, CCl_4). The spectra obtained using (+)-*(6)* as the auxiliary compound showed an additional peak at δ = 5.3 at 1 °C in the case of *(4)* and at δ = 6.0 at 1 °C in the case of *(2)* which seems to be due to H_2O; integration indicates approximately 4 moles H_2O per mole (+)-*(6)*.

[9] For the simulation of line shape, a computer program [*V. Jonas*, Thesis, University of California, Riverside 1970, p. 226] was used, which is based upon the line shape equation of *M. T. Rogers* and *J. C. Woodbrey* [J. Phys. Chem. 66, 540 (1962)]. The width at half height in the absence of fast exchange (1.4 Hz at 30 °C) was measured using a solution which contained racemic (±)-*(1)* instead of (+)-*(1)*; see [1].

[10] For *(2)* in $CCl_4/CFCl_3$ in the presence of (+)-*(6)*, simulations were carried out for spectra which had been obtained at seven temperatures between 21 and 35 °C, yielding $\Delta G^{\neq} = 16.5$ kcal/mol at both 32 and 70 °C ($\Delta H^{\neq} = 16.5$ kcal/mol, $\Delta S^{\neq} = 0$ e. u., 32 °C). In the case of *(4)* in CCl_4 in the presence of (+)-*(6)*, kinetic data were obtained at 10 temperatures between 26 and 53 °C, yielding $\Delta G_c^{\neq} = 16.7$ kcal/mol at 39 °C ($\Delta H^{\neq} = 15.4$ kcal/mol, $\Delta S^{\neq} = -4$ e. u., 39 °C).

A Variation of the Sulfide Contraction Procedure for Synthesis of Corrinoid Systems[**]

By *Erwin Götschi, Walter Hunkeler, Hans-Jakob Wild, Peter Schneider, Walter Fuhrer, John Gleason*, and *Albert Eschenmoser*[*]

The "sulfide contraction procedure" developed during the synthesis of vitamin B_{12} has proved an efficient general method for construction of corrinoid chromophore sys-

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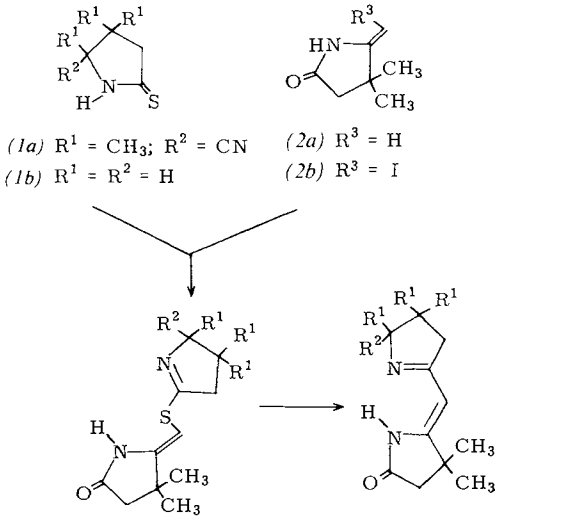
tems[1-4][*]. However, in the condensation of thiolactam derivatives with cyclic enamide systems, cases have also been met in which the original procedure of oxidative coupling by benzoyl peroxide[8] is either unsatisfactory or fails completely. Difficulties of this kind could be overcome by using iodinated enamides, and this alternative method is illustrated by examples below[9].



(1a) $R^1 = CH_3$; $R^2 = CN$ *(2a)* $R^3 = H$
(1b) $R^1 = R^2 = H$ *(2b)* $R^3 = I$

(3a) $R^1 = CH_3$; $R^2 = CN$ *(4a)* $R^1 = CH_3$; $R^2 = CN$
(3b) $R^1 = R^2 = H$ *(4b)* $R^1 = R^2 = H$

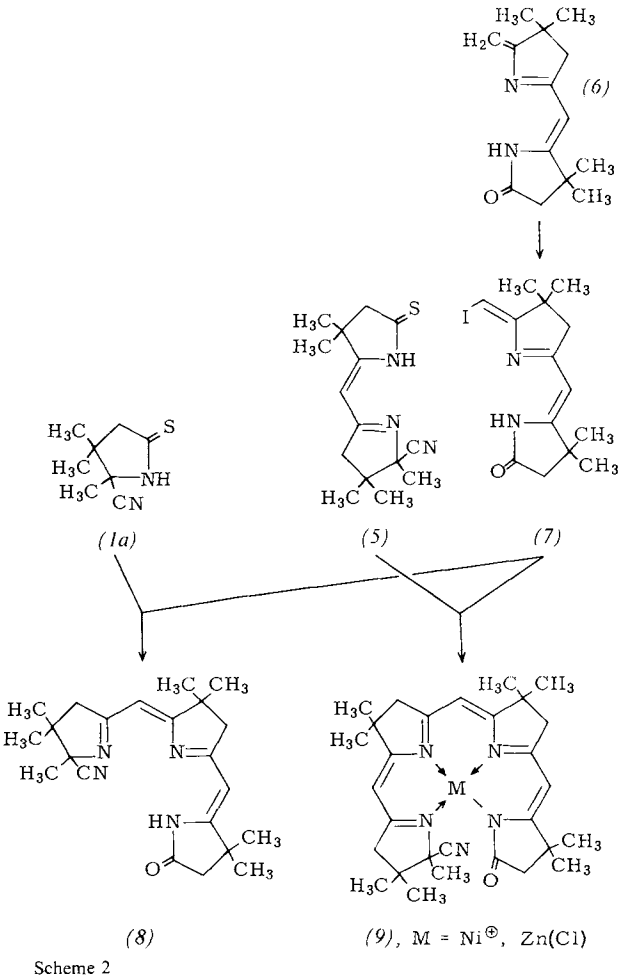
(1a) + *(2a)* $\xrightarrow{A(90\%)}$ *(3a)* $\xrightarrow{C(90\%)}$ *(4a)*
(1b) + *(2a)* $\xrightarrow{A(0\%)}$ *(3b)*
(1a) + *(2b)* $\xrightarrow{B(88\%)}$ *(3a)*
(1b) + *(2b)* $\xrightarrow{B(60\%)}$ *(3b)* $\xrightarrow{C(92\%)}$ *(4b)*

Scheme 1. Method A: 1.0 mol of *(1a)* or *(1b)* + 1.5 mol of *(2a)* + 1.1 mol of dibenzoyl peroxide in benzene; *ca.* 20 C; 24 h [2, 11]. Method B: 1.0 mol of *(1a)* or *(1b)* + 1.0 mol of *(2b)* + 2.0 mol of K *tert*-butoxide in $(CH_3)_3COH$/benzene; *ca.* 20 C; 3 or 15 h, respectively [12]. C: Excess of $(C_2H_5O)_3P$ in xylene; 130 C; 20 h [2, 11, 12].

Whereas oxidative coupling of 4,4-dimethyl-5-methylene-2-pyrrolidone *(2a)*[10] with 5-cyano-4,4,5-trimethyl-2-thiopyrrolidone *(1a)* with dibenzoyl peroxide (method A, Scheme 1) gives the thioether *(3a)* in excellent yield, this method fails on attempted coupling of *(2a)* with the unsubstituted 2-thiopyrrolidone *(1b)*. The cause of this failure is undoubtedly the (experimentally demonstrated) extreme lability of the unsubstituted bisimidoyl disulfide[2] that is derived from thiopyrrolidone *(1b)*, which would have to act as mediator for the coupling reaction; the substituted analog from *(1a)*, namely *(12)*, is much more stable[2].

The alternative procedure B (see Scheme 1) is successful in both these cases. Here, 5-(iodomethylene)-4,4-dimethyl-2-pyrrolidone *(2b)* [prepared from the enamide *(2a)* by iodination][13] is treated with the thiopyrrolidone reactant *(1)* in the presence of a strong base, bringing about the (formal) displacement of the vinylically bound iodine by the thiolactam-sulfur. The bromo derivative undergoes this replacement reaction only to a very limited extent. The contraction to the "semicorrinoid" system *(4b)* occurs in excellent yield when *(3b)* is heated in presence of triethyl phosphite, as in the case *(3a)* → *(4a)* described previously[2]. The new compound *(4b)* is an intermediate in the synthesis of a 1-hydroxycorrin derivative[14].

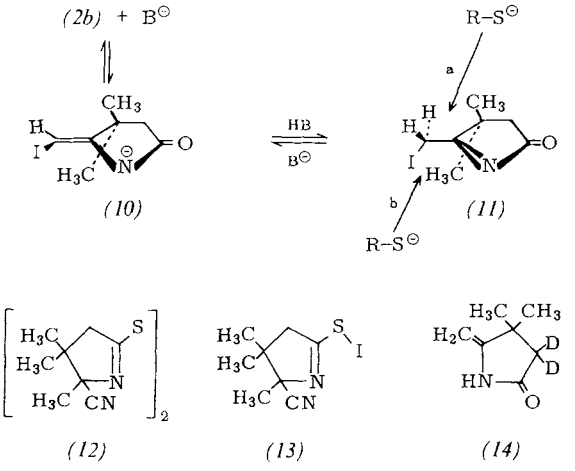
[*] A completely different method for the construction of corrinoid chromophoric systems has been described recently by *G. Traverso et al.* [5] and by *R. V. Stevens et al.* [6]. For *A. W. Johnson*'s route to corrin complexes see [7].



Scheme 2

The wide applicability and superiority of the new procedure is further illustrated by the examples shown in Scheme 2. The base-induced coupling of the bicyclic iodoenamide *(7)*[15] with the thiopyrrolidone derivative *(1a)* by method B occurs in 70% yield[12]; the contraction of the product to the tricyclic system *(8)* has been described previously[2]. Finally the procedure provides a simple synthesis of more complicated *seco*-corrinoid systems such as the tetracyclic complexes *(9)*. Coupling the bicyclic reactants *(5)* and *(7)* in acetonitrile at room temperature in the presence of 1,5-diazabicyclo[5.4.0]undec-5-ene proceeds in 64% yield[16]; in this case, the subsequent contraction to *(9)* with triphenylphosphane is clearly assisted by complexation, for it occurs remarkably readily in the presence of nickel or zinc perchlorate (50 C; 2 h; spectroscopic yields 76 and 83%; isolated 63 and 65%, respectively[12]). The complex *(9)* is of interest with regard to the synthesis of metal-free corphin derivatives[17].

The reaction mechanism for this base-induced coupling of thiolactam derivatives with iodinated enamide systems is as complex as its preparative realization is simple. The course of the reaction envisaged originally as a working hypothesis was initial base-induced tautomeric equilibration *(2b)* ⇌ *(10)* ⇌ *(11)* (see Scheme 3) of the iodoenamide, followed by rapid trapping of the unstable isomer *(11)* in an S_N2 reaction by the thiolactam-sulfur at the iodomethyl-carbon atom (path a[1-4]). However, in the case of the change *(1a)* + *(2b)* → *(3a)* this route contributes only very little, if at all, to product formation. Following the course of the reaction by NMR spectroscopy disclosed that in the initial phase of the reaction small amounts (*ca.* 10 mol-%) of the bisimidoyl disulfide *(12)* and of



Scheme 3

the iodine-free enamide *(2a)* are rapidly formed; the concentration of the latter remains stationary, but *(12)* disappears again towards the end of the reaction. Experiments with equimolar amounts of the components *(1a)*, *(2b)*, and dideuterioenamide *(14)* led to incorporation of up to 50% of the deuterated enamide in the product *(3a)*[18]. In the absence of the reactant *(1a)* the iodoenamide *(2b)* is effectively stable under the reaction conditions, but it is almost completely deuterated at the vinyl position under similar conditions in the presence of *O*-deuterio-*tert*-butyl alcohol. Treating the iodoenamide *(2b)* with two equivalents of the thiolactam *(1a)* in benzene containing one equivalent of 1,4-diazabicyclo[2.2.2]octane at room temperature for 8 h gives none of the coupling product *(3a)* but, instead, a 79% yield of the disulfide *(12)* along with the enamide *(2a)*.

These observations support the view that the iodoenamide tautomer *(11)* undergoes mainly a *reductive* displacement of iodine (path b) and that formation of the coupling product *(3a)* occurs chiefly by reaction of the deprotonated enamide *(2a)* with the oxidation products *(13)* and/or *(12)* of the thiolactam. However, this mechanism of thiolactam-iodoenamide coupling must be very sensitive to reaction conditions and structural features; this is shown by the finding that reaction of the bicyclic iodoenamide *(7)* with the thiopyrrolidone derivative *(1a)* in the presence of one equivalent of the enamide *(2a)* and 3 equivalents of potassium *tert*-butoxide affords only the tricyclic coupling product *(8)* (62%) and *none* of the bicyclic product *(3a)*. Since it is known from a control experiment that under such conditions the monocyclic enamide *(2a)* is much more reactive than the bicyclic iodine-free enamide *(6)* towards the disulfide *(12)*[2], it must be concluded that the disulfide *(12)* does *not* act as coupling mediator in the reaction *(1a)* + *(7)* → *(8)* (Scheme 2), although it appears to do so in process *(1a)* + *(2b)* → *(3a)* (Scheme 1). It remains undecided whether, among other possibilities, the former reaction proceeds by the alternative path a (Scheme 3) or whether initial displacement *via* path b is followed by direct coupling of species *(13)*.

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[7] *A. W. Johnson* and *W. R. Overend*, Chem. Commun. *1971*, 710; J. C. S. Perkin I *1972*, 2681; cf. also *H. H. Inhoffen, J. Ulrich, H. A. Hoffmann*, and *G. Klinzmann*, Tetrahedron Lett. *1969*, 613.

[8] *B. Golding* and *P. Löliger*; cf. *P. Löliger*, Dissertation, ETH Zürich 1968.

[9] For the development of this procedure in the synthesis of vitamin B_{12} see [1], also *P. Schneider*, Dissertation, ETH, Zürich 1972, and *W. Fuhrer*, Dissertation, ETH Zürich, 1973.

[10] *E. Bertele, H. Boos, J. D. Dunitz, F. Elsinger, A. Eschenmoser, I. Felner, H. P. Gribi, H. Gschwend, E. F. Meyer, M. Pesaro*, and *R. Scheffold*, Angew. Chem. *76*, 393 (1964); Angew. Chem. internat. Edit. *3*, 490 (1964).

[11] *H.-J. Wild*, Dissertation, ETH Zürich 1972.

[12] *E. Götschi*, Dissertation, ETH Zürich 1973.

[13] Iodination of *(2a)* with 1.0 equiv. of I_2 in ether in presence of solid K_2CO_3 at room temperature affords 87% of *(2b)*, m.p. 88 °C, λ_{max} = 238 nm (ε = 14200) in C_2H_5OH; δ = 1.30 (s, $2CH_3$), 2.50 (s, CH_2), 4.93 (s, CH), 7.6 (br., NH) ppm in $CDCl_3$; ν̄NH in CCl_4 at $c \leqslant 6.6 \times 10^{-3}$ mol/l = 3410 cm^{-1} (sharp, no intermolecular H-bonding). Iodination of *(2a)* with 2.0 equiv. of I_2 affords the diiodide, m.p. 144 °C; δ(CH_3) = 1.58 ν̄NH in CCl_4 at $c \leqslant 6.6 \times 10^{-3}$ mol/l = 3395 cm^{-1} (sharp). Reduction of the diiodide with $(C_6H_5)_3SnH$/pyridine in $CDCl_3$ at 45 °C gives, along with *(2b)*, the (NH/I)-*trans*-monoiodide, m.p. 105 °C, λ_{max} = 240 nm (ε = 18700); δ = 1.54 (s, $2CH_3$), 2.47 (s, CH_2), 5.24 (s, CH), 8.7 (br., NH) ppm; ν̄NH in CCl_4 at $c \geqslant 6.6 \times 10^{-4}$ mol/l = 3430 (sharp) and 3170 (br.) cm^{-1} (concentration-dependent, intermolecular H-bonding). This *trans*-monoiodide isomerizes very rapidly and completely into *(2b)* on contact with acids or bases.

[14] Cf. *E. Götschi* and *A. Eschenmoser*, Angew. Chem. *85*, 952 (1973); Angew. Chem. internat. Edit. *12*, 912 (1973).

[15] Prepared by treatment of *(6)* [10, 2, 5, 6] with iodosuccinimide in benzene/$(CH_3)_3COH$ at room temperature for 30 min; yield 81% [12]. The physical data for *(7)* are given in [14].

[16] It is possible to obtain this coupling product from the bisimidoyl disulfide produced from *(5)* by benzoyl peroxide, but that method is preparatively unsatisfactory; cf. *P. Wehrli*, Dissertation, ETH, Zürich 1967.

[17] Cf. *P. Müller, S. Farooq, B. Hardegger, W. Salmond*, and *A. Eschenmoser*, Angew. Chem. *85*, 954 (1973); Angew. Chem. internat. Edit. *12*, 914 (1973). Data for *(9)* are given therein.

[18] Under such reaction conditions, at most *ca.* 5% of the iodine of *(2b)* is transferred to *(14)* [NMR spectroscopic D-analysis of recovered *(2b)* in a control experiment without *(1a)*]. Deuterium in the position a to the lactam group of *(2a)*, unlike that in the vinyl position, is resistant to exchange under the reaction conditions. Detailed descriptions of the experiments referring to the mechanism of the coupling reaction are given by *E. Götschi* [12].

Formation of a 1-Hydroxycorrin complex by Photochemical A/D-Secocorrin → Corrin Cycloisomerization[**]

By *Erwin Götschi* and *Albert Eschenmoser*[*]

Light-induced cycloisomerization of A/D-secocorrin complexes *(1)* → *(2)* is the key step in a type of corrin synthesis

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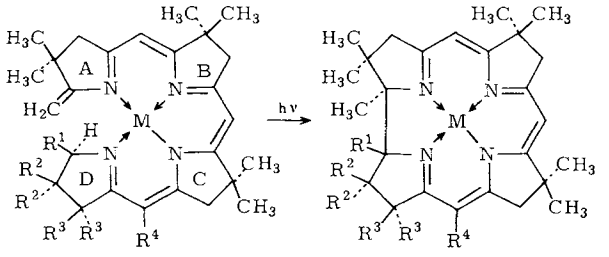
[**] This work was supported by the Schweizerischer Nationalfonds zur Förderung der wissenschaftlichen Forschung.

that has served for the preparation of a series of basic derivatives of this ligand system[1,2] and later proved its value in one of the two synthetic routes to vitamin B_{12}[3].



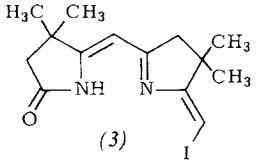
(1) (2)

Scheme 1.

	R^1	R^2	R^3	R^4	M
a	H	H	H	CN	Zn(Cl), Mg(Cl), Cd(Cl) Li, Pd^+, Pt^+ [1, 2]
b	H	1/2—O—CH_2—CH_2—O—	H	CN	Pd^+ [4a]
c	H	H	CH_3	H	Zn(Cl) [4b]
d	$COOCH_3$	H	H	CN	Cd(Cl) [4c]

Our experience with this photochemical ring-closure indicates that it has considerable preparative scope; in the series of methyl-substituted corrin systems the reaction has so far been successful in the cases *a–d* summarized in Scheme 1[1,2,4]. The recent variation[5] in the synthesis of corrinoid chromophore systems has now made it possible to examine the question[6] whether this ring closure also occurs if the secocorrinoid reactant contains a carbonyl double bond instead of the exocyclic methylene double bond on ring A [cf. *(1)*]. The synthesis of *rac.*-1-hydroxy-3,3,8,8,13,13-hexamethylcorrin-chlorozinc complex *(6)* outlined in Scheme 2 provides the answer to this question.

Under comparable conditions of irradiation, cycloisomerization of the 1-oxo-A/D-secocorrin complex *(5)* is distinctly



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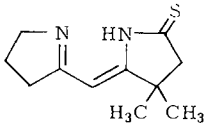

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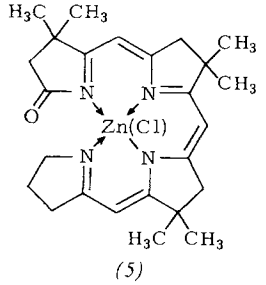

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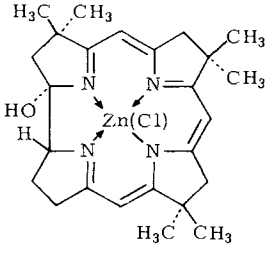

(6)

(racem)

(3) [5]:
m. p. 140 °C
228 (8900), 237 (10300), 345 (13100) nm (C_2H_5OH); *inter alia*, 3300—3100w, 1738s/1724s, 1633s, 1610m, 1515s, *etc.*, cm^{-1} ($CHCl_3$)
1.23/1.37 (2s, each 6H), 2.43/2.79 (2s, each 2H), 5.14/5.55 (2s, each 1H), 11.4—11.6 (br., 1H) ($CDCl_3$)
inter alia 358 (66%, M^+), 343 (100%, $M^+ - CH_3$)

(4) [8]:
m. p. 87 °C

a) 1.0 *(3)* + 1.0 *(4)* + 8 equiv. 1,5-diazabicyclo[5.4.0]undec-5-ene [9] in CH_3CN; room temp. under argon; chromatography of the coupling product (yield *ca.* 50%)
b) +1.5 $(C_6H_5)_3P$ + 1.0 $Zn(ClO_4)_2$ in CH_3CN; 1 h; 50 °C (*ca.* 60% cryst.).

(5):
265 (26500), 268 (sh, 11800), 299 (sh, 17200), 326 (sh, 37500), 333 (28200), 363 (7100), 381 (4900), 510 (14000) nm (C_2H_5OH); *inter alia* 1712m, 1642w, 1607s, 1592s, 1516s, 1489s cm^{-1} ($CHCl_3$)
1.27/1.30/1.37 (3s, each 6H), 1.68—2.06 (m, 2H), 2.36 (s, 2H), 2.72/2.78 (2s + m, total 6H), 3.80—4.10 (m, 2H), 5.30/5.37/5.40 (3s/each 1H) ($CDCl_3$)
inter alia 469 (13%, $M^+ - Cl/^{64}Zn$), 468 (25%, $M^+ - HCl$), 453 (100%, $M^+ - HCl - CH_3{}^{64}Zn$)
hv (high-pressure lamp, 70W Pyrex filter in benzene, under argon, *ca.* 40 °C (89%)

(6):
262 (28600), 305 (sh, 28200), 317 (51500), 378 (sh, 1900), 483/498 (12900) nm (C_2H_5OH); 259 (29100), 300 (sh, 30400), 311 (45100), 354 (6800), 377 (sh, 4300), 481 (12200), 504 (13100) nm (C_2H_5OH + 1 drop N HCl per 5 ml of solution = spectrum of the decomplexed, protonated ligand)
inter alia 3395w (broad), 1620w, 1576s, 1562s, 1508s, 1488m cm^{-1} ($CHCl_3$)
1.20/1.24/1.30/1.43 (4s, each 3H), 1.35 (s, 6H), 1.99/2.15 (AB system, J = 14 Hz superimposed by m at 1.95—2.46, total 4H), 2.57—3.10 (m, superimposed by s at 2.79, total 6H), 3.52—3.78 (tripletoid m, 1H), 3.98 (s, 1H, disappears on deuterium exchange with D_2O), 5.22/5.24/5.40 (3s, each 1H) ($CDCl_3$)
inter alia 490 (3%), 488 (5%), 486 (5%, $M^+ - H_2O/^{64}Zn$, ^{35}Cl), 468 (12%, $M^+ - HCl$), 450 (100%, $M^+ - H_2O - HCl$), 435 (92%, $M^+ - H_2O - HCl - CH_3$), 234 (5%, $M^{2+} - HCl$), 225 (16%, $M^{2+} - H_2O - HCl$).

Scheme 2. Spectroscopic data for *(3)*, *(4)*, *(5)*, and *(6)*. Data are arranged in the order: λ_{max} (ε in brackets; selected bands from the IR spectra; signals of the proton resonance spectrum (δ values referred to δ(TMS) = 0 ppm); selected signals from the mass spectrum. The compounds formulated were isolated in crystalline form, homogeneous on thin-layer chromatography, and gave correct analytical data. Detailed directions are available in [7].

slower than that of the 1-methylene analogs *(1a)* (M = ZnCl) and *(1c)*. Here, as in comparable cases, rigorous exclusion of air is a prerequisite for the success of this cycloisomerization (yield up to 89%); oxygen inhibits the photocyclization of secocorrinoid zinc complexes very effectively[2] and also affects the product (presumably by oxidation)[10].

Assignment of constitution to the irradiation product *(6)* is based on the characteristic spectral changes (UV/VIS, IR, ^{1}H-NMR, and MS) in going from the educt to the product, and on the significant correspondence of spectroscopic data for the product with those of known corrin complexes of analogous structure, especially *(2c)*. When compared with that of the educt the electronic spectrum of *(6)* shows the expected hypsochromic shifts, and corresponds to the spectrum of the chlorozinc-corrin complex *(2c)* with respect to both position and structure of the absorption bands[11]. The IR spectrum shows an absorption in the $\tilde{\nu}$(OH) region[12] and lacks the carbonyl band of the educt; the absorption pattern in the structure-sensitive chromophore stretching region between 1650 and 1480 cm^{-1} agrees with that in the spectrum of complex *(2c)*[11]. A tripletoid one-proton signal at 3.65 ppm in the ^{1}H-NMR spectrum of *(6)* reveals the presence of the tertiary CH group created by the ring closure; the spectrum also shows an OH singlet at 3.98 ppm identified by deuterium exchange. Finally the structural change *(5)* → *(6)* is also reflected in the expected manner in the mass spectra of the two compounds (cf. Scheme 2).

The configuration of the linkage between rings A and D in *(6)* is assumed to be *anti* in analogy with the known steric outcome of the reactions *(1)* → *(2)*; the close correspondence of the UV/VIS and IR spectroscopic data of *(6)* and *(2c)* supports this assignment. However, further studies are needed to decide whether the light-induced ring closure *(5)*—*(6)* is a simple oxa analog of the reaction type *(1)*—*(2)*, not only from a constitutional, but also from a mechanistic point of view.

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[2] *H.-J. Wild*, Dissertation, ETH Zürich 1972.

[3] a) *A. Eschenmoser*, Pure Appl. Chem. Suppl. XXIII IUPAC Congress Boston, Vol. 2, 69 (1971); b) *R. B. Woodward*, Pure Appl. Chem. *33*, 145 (1973); c) *W. Fuhrer, P. Schneider, W. Schilling, H.-J. Wild, H. Maag, N. Obata, A. Holmes, J. Schreiber*, and *A. Eschenmoser*, Chimia *26*, 320 (1972).

[4] a) *G. Kloster*, Dissertation ETH Zürich, 1973; b) *J. Gleason, B. Place*, and *A. Eschenmoser*, unpublished work; cf. [3a]; c) *N. Bühler*, Dissertation ETH, Zürich, 1973.

[5] *E. Götschi, W. Hunkeler, H.-J. Wild, P. Schneider, W. Fuhrer, J. Gleason*, and *A. Eschenmoser*, Angew. Chem. *85*, 950 (1973); Angew. Chem. internat. Edit. *12*, 910 (1973).

[6] This question was posed by *E. Götschi (A. E.)*.

[7] *E. Götschi*, Dissertation, ETH Zürich 1973.

[8] Prepared from the corresponding lactam and 1.5 equiv. of P_2S_5 in toluene/4-methylpyridine (20:1); 4 h; *ca.* 130 °C; yield 75% (cf. [7]).

[9] *H. Oediger* and *F. Möller*, Angew. Chem. *79*, 53 (1967); Angew. Chem. internat. Edit. *6*, 76 (1967).

[10] Chlorozinc-corrin complexes are efficient sensitizers for singlet oxygen reactions (*A. Rüttimann*, Dissertation, ETH Zürich, 1973).

[11] Data of *(2c)* for comparison [4b]: λ_{max} = 261 (32500), 308 (sh, 33600), 317 (55500), 371 (sh, 2000), 473 (14400), 496 (14200) nm (CH_3OH). $\tilde{\nu}$ = *inter alia*, 1618w, 1577s, 1565s, 1508s, 1494m cm^{-1} ($CHCl_3$).

[12] The position and broad structure of this band indicate H-bonding of the hydroxyl group. A hydrogen bond to the chloride ligand seems possible in the (OH/Cl)-*cis*-configuration.

Metal-Free Derivatives of the Corphin Ligand System[**]

By *Peter M. Müller, Saleem Farooq, Bruno Hardegger, William S. Salmond*, and *Albert Eschenmoser*[*]

Metal-free derivatives of the corrin ligand system can be obtained from corrin complexes containing metal ions such as those of zinc, cadmium, or magnesium that are easily displaced by acidolysis[1]. However, there is still no method of removing transition-metal ions such as those of nickel, cobalt, palladium or platinum from their robust complexes with the corrin ligand without destruction of the latter. The same is true for the corresponding derivatives of the corphin ligand system[3], where the first member was obtained as a palladium complex[2]. We report here a process by which metal-free derivatives of this corrinoid-porphinoid structural type now become accessible[4].

The complexes *(1a)* and *(1b)* can be readily prepared by the iodoenamide-thiolactam coupling procedure (cf. Scheme 1)[5]. The cyanide protecting group can be removed in high yield from the nickel complex *(1a)* by treatment with potassium *tert*-butoxide to give the precorphinoid complex *(2a)*. Under carefully controlled conditions the nickel in *(2a)* can be replaced by zinc through treatment with potassium cyanide and, immediately thereafter, complexing with zinc perchlorate; the unstable zinc complex *(2b)* is not isolated in pure form but can be cyclized directly to the chlorozinc-corphin complex *(3a)* by alkylation with triethyloxonium tetrafluoroborate in the presence of ethyldiisopropylamine. A more direct sequence, that of decyanidation → cyclization starting from the cyanide-protected zinc complex *(1b)* is also feasible, but this formally shorter route proved preparatively delicate and less reliable[4].

The precorphinoid palladium complex *(2c)* has been described previously in connection with the original synthesis of the palladium-corphin complex *(3c)*[2]. The transcomplexation-cyclization step *(2)* → *(3)* proved just as successful with this palladium complex *(2c)* as with the corresponding nickel derivative; thus the chlorozinc complex *(3a)* can now be obtained in two ways. The two routes differ, however, in that the old one is limited to the synthesis of corphin derivatives of centrosymmetric structure, *e.g.* *(3)*[6], whereas the route involving iodoenamide-thiolactam coupling can in principle also serve for the synthesis of corphin ligands with asymmetrical structure.

The chlorozinc-corphin complex *(3a)* is recovered almost unchanged under the mild conditions that suffice to decomplex the corresponding corrin complexes (trifluoroacetic acid in acetonitrile). However, acidolytic decomplexation can be smoothly effected with concentrated hydrochloric acid at room temperature. The corphinium ion *(4)* can be isolated as chloride, bromide, or perchlorate in crystalline form. The structure assigned to it is best illustrated by the proton resonance spectrum, in which four proton types are evident as singlets in the intensity ratio 2:5:6:24. On forward titration with tetramethylammonium hydroxide in methylcellosolve-water (4:1 w/w) the corphinium ion *(4)* shows an apparent pK_{MCS} value

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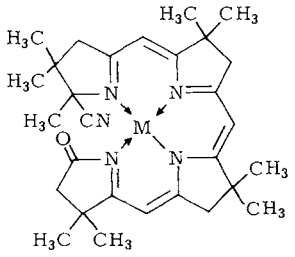
[**] This work was supported by the Schweizerischer Nationalfonds zur Förderung der wissenschaftlichen Forschung.



(1a), M = $Ni^{\oplus}(ClO_4^{\ominus})$[5]
(1b), M = Zn(Cl)[5]

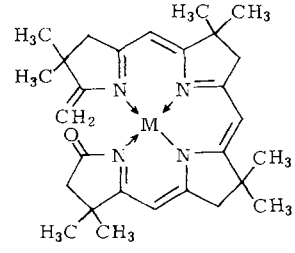
(1a), M = Ni^+:
m.p. 220 °C (dec.)
275 (18700), 339 (13200), 399 (3300 m, flat), 492 (10200) nm in C_2H_5OH

inter alia 1747m, 1628w, 1602m, 1558s, 1510s, *etc.* cm^{-1} in $CHCl_3$
0.99/1.24/1.44/2.15 (4s/each, $1CH_3$), 1.27 (s, $2CH_3$), 1.49 (s, $3CH_3$), 2.2—2.5 (m, 8H), 5.88/6.14/6.21 (3s, each 1H) ppm in $CDCl_3$

inter alia 529 (6%, $M^+ - HClO_4/^{58}Ni$), 514 (30%, $M^+ - HClO_4 - CH_3$), 502 (24%, $M^+ - HClO_4 - HCN$), 487 (100%, $M^+ - HClO_4 - HCN - CH_3$)

(1a)

ca. 6 equiv. *t*-BuOK in *t*-BuOH; 1.5 h; *ca.* 80 °C; N_2 (93%)



(2a), M = $Ni^{\oplus}(ClO_4^{\ominus})$
(2b), M = Zn(Cl)
(2c), M = $Pd^{\oplus}$[2]

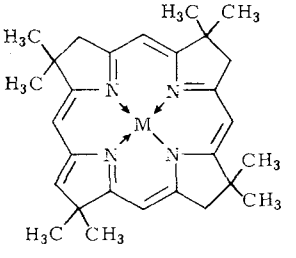
(2a), M = Ni^+:
m.p. 170—172 °C (dec.)
256 (18500), 276 (21300), 346 (18700), 493 (9900) nm in C_2H_5OH

inter alia 1746m, 1628m, 1603s, 1550s, 1510s, *etc.* cm^{-1}
1.15/1.18/1.30/1.33/1.40/1.45 (6s, each $1CH_3$), 1.50 (s. $2CH_3$), 2.43/2.83 (d, $J \approx 2$ Hz)/3.14/3.34 ($4CH_2$), 4.76/5.10 (2d, $J = 3.5$ Hz, each 1H), 5.93/6.25/6.33 (3s, each 1H) ppm in $CDCl_3$

inter alia 502 (21%, $M^+ - HClO_4/^{58}Ni$), 487 (100%, $M^+ - HClO_4 - CH_3$)

(2a) or *(2c)*

30 equiv. KCN in CH_3OH, 10 min, room temp. → +30 equiv. $Zn(ClO_4)_2 \cdot 6H_2O$ → *(2c)* worked up → +15($(C_2H_5)_3O^+BF_4^-$ +5 ethyldiisopropylamine, CH_2Cl_2, 19 h, room temp. (33%)



(3a), M = Zn(Cl)
(3b), M = $Ni^{\oplus}$[4]
(3c), M = $Pd^{\oplus}$[2]
(3d), M = $Co(CN)_2$[4]

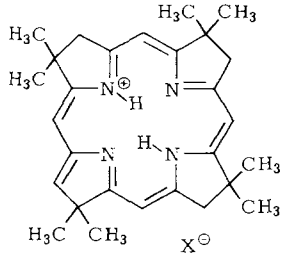
(3a), M = Zn(Cl):
m.p. *ca.* 260 °C (dec.)
227 (13400), 248—256 (13200), 263 (13400), 294 (sh, 38000), 302 (47600), 343 (sh, 39600), 353 (48200), 384 (sh, 7100), 410 (4900), 462 (sh, 6800), 531/547 (broad double max., 9900/9700) nm in C_2H_5OH

inter alia 1661w, 1634m, 1611s, 1569w, 1537s, 1502s, *etc.* cm^{-1} in $CHCl_3$
1.35 (s, br., $8CH_3$), 2.88/2.92 (m, $3CH_2$), 5.49 (s, 2H), 5.72/5.78/6.00 (3s, each 1H) ppm in $CDCl_3$

inter alia 526 (11%, $M^+/^{64}Zn/^{35}Cl$), 491 (100%, $M^+ - Cl/^{64}Zn$), 490 (47%), 476 (85%, $M^+ - Cl - CH_3/^{64}Zn$), 475 (46%), *etc.*

(3a)

a) *ca.* 37% HCl/H_2O; room temp.; 1 h → *(4a)* (80%)
b) Work up with satd. KBr solution containing HBr → *(4b)* (73%)



(4a), X = Cl
(4b), X = Br
(4c), X = ClO_4

(4b), X = Br:
m.p. 234 °C (dec.) from CH_2Cl_2—C_6H_6
295 (46100), 321 (sh, 39000), 332 (42000), 346 (38500), 381 (sh, 7000), 404 (4500), 530 (16500) nm in C_2H_5OH + 1 drop CF_3COOH per 25 ml (spectrum in $CHCl_3$ very similar)

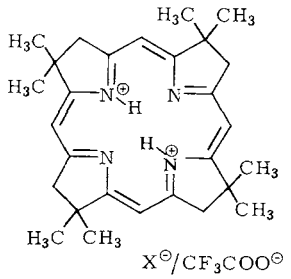
inter alia 3300w,br., 2445w,br., 1666s, 1644m, 1616s, 1565s, 1502s, *etc.* cm^{-1} in $CHCl_3$

(4a)-*(4c)*
in CF_3COOH

1.37/1.47/1.48/1.50 (4s, each $2CH_3$), 3.06/3.17/3.27 (3s, each $1CH_3$), 5.86/5.90/6.10/6.24/6.29 (5s, each 1H), 10.1 (s,br., *ca.* 2H) ppm in $CDCl_3$

inter alia 429 (20%), 428 (55%, $M^+ - HBr$), 413 (100%, $M^+ - HBr - CH_3$), *etc.*

pK^+_{MCS} (Ref. [7]) = 7.3; equiv. wt. found 513 (calc. 509)



$X^{\ominus}/CF_3COO^{\ominus}$

(5)

(5), X = ClO_4:
290 (14000, sh), 308 (35000, sh), 321 (75000, max), 332 (43600, min), 340 (51500, sh), 353 (90500, max), 375 (36600, min), 376 (36700, max), 387 (28800, min), 393 (30600, max), *ca.* 450 (*ca.* 750, flat min), *ca.* 500 (*ca.* 1000, flat max) nm in CF_3COOH

1.34/2.79/5.47 (3s, intensity ratio 6:2:1); also m at 1.6 ppm (*ca.* 10% impurities) in CF_3COOH

Scheme 1. Properties of compounds of types *(1)*, *(2)*, *(3)*, *(4)*, and *(5)*. Spectroscopic data in the following order: λ_{max} (ε in brackets); selected bands from the IR spectra; signals from the proton resonance spectrum (δ values referred to δ(TMS) = 0 ppm); selected signals from the mass spectra. Except for *(2b)* and *(5)*, all the compounds formulated were obtained in homogeneous crystalline form and gave correct analytical values. Detailed description of the experiments can be found in [4].

of *ca.* 7.3, approximately comparable with that of a carboxylic acid[8]. Treatment of *(4a)* with nickel acetate in boiling acetonitrile gives the nickel complex *(3b)*, isolated as its crystalline perchlorate; with cobalt(II) chloride[9] in the presence of sodium acetate in methanol at 50 °C, the dicyanocobalt(III)-corphin complex *(3d)* can easily be obtained following work up with cyanide in contact with air[10].

The complexes *(3a)* and *(3c)*, as well as the metal-free corphinium ion *(4)*, exist in trifluoroacetic acid as derivatives of the more highly symmetrical (*trans-cis*)$_4$-1,5,9,13-tetraaza[16]annulene system *(5)*; in trifluoroacetic acid their proton resonance spectra are reduced to three singlets[11] and the corresponding electronic spectra show unambiguously the presence of a non-corrinoid chromophore in this solvent [cf. data for *(5)* in Scheme 1]. The signals of the vinyl and methylene protons of the *doubly* positively charged tetraazaannulene system *(5)* are at distinctly *higher* field than the corresponding groups of signals from the *singly* positively charged corphinium ion *(4)*[12]; the interpretation of this shift as an effect of a paramagnetic ring current[13] in the pericyclically conjugated $4n$-π-system *(5)* constitutes specific support for the structural assignment.

New experimental findings[14] concerning the biosynthesis of vitamin B_{12} have caused us to lose confidence in a hypothesis we have cherished for a number of years, namely, that the corphin ligand system might play a role in the biosynthesis of naturally occurring corrinoids[2]. Fortunately, however, the compounds of type *(5)* merit interest as the porphinoid representatives of the heteroanalogs of carbocyclic annulenes[15].

Received: July 10, 1973 [Z 889 IE]
German version: Angew. Chem. *85*, 954 (1973)

[1] *A. Fischli* and *A. Eschenmoser*, Angew. Chem. 79, 865 (1967); Angew. Chem. internat. Edit. 6, 866 (1967); *A. Eschenmoser*, Quart. Rev. Chem. Soc. *24*, 366 (1970); *H.-J. Wild*, Dissertation, ETH Zürich 1972.

[2] *A. P. Johnson*, *P. Wehrli*, *R. Fletcher*, and *A. Eschenmoser*, Angew. Chem. *80*, 622 (1968); Angew. Chem. internat. Edit. 7, 623 (1968).

[3] A zinc(II) octaethylphenylhexahydroxycorphin derivative has been described by *H. H. Inhoffen* and *N. Müller* (Tetrahedron Lett. *1969*, 3209).

[4] Cf. *P. M. Müller*, Dissertation ETH Zürich, 1973.

[5] *E. Götschi*, *W. Hunkeler*, *H.-J. Wild*, *P. Schneider*, *W. Fuhrer*, *J. Gleason*, and *A. Eschenmoser*, Angew. Chem. *85*, 950 (1973); Angew. Chem. internat. Edit. *12*, 910 (1973).

[6] The yields of the palladium complexes denoted as *(6)* and *(8)* in [2] have meanwhile been considerably improved; *(8)* can be obtained in about 60% yield from the *trans*-precursor complex *(6)*, and *(6)* can be prepared in 85% yield by light-induced isomerization of the corresponding *cis*-complex (*(5)* in [2]); for details see [4].

[7] Cf. *W. Simon*, Helv. Chim. Acta *41*, 1835 (1958).

[8] According to the UV spectrum, the deprotonation probably leads to a mixture of peripherally deprotonated neutral products; these were very sparingly soluble and were not further investigated.

[9] Cf. *R. B. Woodward*, Pure Appl. Chem. *25*, 283 (1971).

[10] The properties of the complexes *(3b)* and *(3d)* are described in detail in [4].

[11] For complete exchange of the methylene protons of the palladium complex *(3c)* by deuterium in deuteriotrifluoroacetic acid see [2].

[12] The same is true for the complexes *(3a)* [4] and *(3c)* [2] in CF_3COOH. The system *(5)* is stable for at least some hours in pure trifluoroacetic acid at room temperature; however, on addition of stronger acids, such as sulfuric or perchloric acid, rearrangement occurs (presumably tautomerization), whose interpretation requires further investigation.

[13] *J. A. Pople* and *K. G. Untch*, J. Amer. Chem. Soc. *88*, 4811 (1966); cf. *F. Sondheimer*, Accounts Chem. Res. *5*, 81 (1972); *J. F. M. Oth* and *J.-M. Gilles*, Tetrahedron Lett. *1968*, 6259.

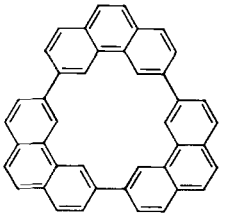
[14] *C. E. Brown*, *J. J. Katz*, and *D. Shemin*, Proc. Nat. Acad. Sci. USA 69, 2585 (1972); *A. I. Scott*, *C. A. Townsend*, *K. Okada*, *M. Kajiwara*, *P. J. Whitman*, and *R. J. Cushley*, J. Amer. Chem. Soc. *94*, 8267, 8269 (1972).

[15] A porphinoid hexaaza-analog of [16]annulene has been prepared by *R. Scheffold* and *J. Löliger* [personal communication from *R. Scheffold*; cf. *J. Löliger*, Dissertation, Fribourg (Switzerland) 1971].

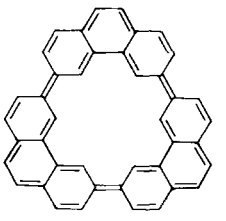
Cyclooctadeca[*cdefg*]phenanthrene ("[18]Annuleno[*cdefg*]phenanthrene")[1]

By *Ute Meissner*, *Bernd Meissner*, and *Heinz A. Staab*[*]

In 3,3′:6′,3″:6″,6-triphenanthrylene *(1)* the annulene conjugation that can be formulated as *(1a)*↔*(1b)* is completely suppressed in favor of π-interaction within the phenanthrene units: the ^{1}H-NMR spectrum does not show any diamagnetic ring current in the macrocyclic system but is in accordance with the existence of three largely unperturbed phenanthrene units[2].



(1a)



(1b)

In connection with the problem of the perturbation of annulenes by condensation with benzenoid systems we became interested in cyclooctadeca[*cdefg*]phenanthrene

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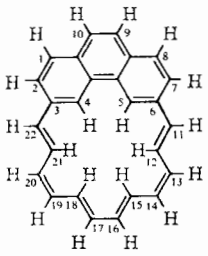
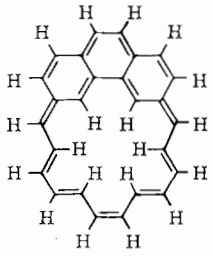
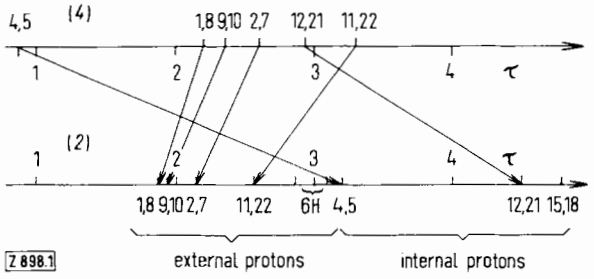


(2a)[3]



(2b)

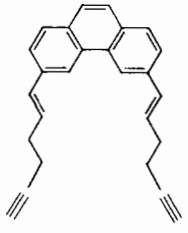


Z 898.1

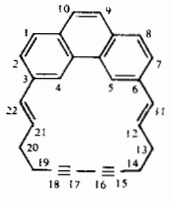
Fig. 1. Comparison of the ^{1}H-NMR spectra of *(4)* and *(2)*.

(2), in which the annulene conjugation competes with only *one* benzenoid phenanthrene unit.

For the synthesis of *(2)*, 3,6-dimethylphenanthrene was prepared from 4,4'-dimethyl-*trans*-stilbene (Hg high-pressure lamp, 0.01 M solution in 5:1 cyclohexane/benzene; iodine; 61% yield) or from 2-(4'-methylphenethyl)magnesium bromide and 4-methylcyclohexanone *via* 4-methyl-1-(4'-methylphenethyl)cyclohexanol[4] and 1,2,3,4,4a,9,10,10a-octahydro-3,6-dimethylphenanthrene (overall yield 25%). Successive conversion into 3,6-bis(bromomethyl)phenanthrene[4] (NBS/CCl_4, 57% yield) and 3,6-bis(triphenylphosphoniomethyl)phenanthrene dibromide[4] (triphenylphosphane/acetonitrile, 80% yield), and a double Wittig reaction with 4-pentynal[5] afforded 3,6-bis(1-hexen-5-ynyl)phenanthrene *(3)* (45% yield)[4], which was cyclized in 50% yield to the 18-membered ring system *(4)*[4] by copper(II) acetate in dimethylformamide. Isomerization with potassium *tert*-butoxide in *tert*-butyl alcohol/benzene finally yielded *(2)*[4] as red crystals (from cyclohexane; dec. above 200 °C; 48% yield).



(3)



(4)

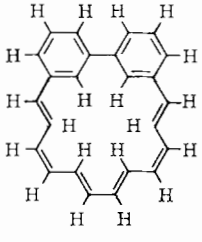
The ^{1}H-NMR spectrum of *(2)* contains the following absorptions (220 MHz, CS_2)[6]: $\tau = 1.87$ and 2.15 (AB system, $J_{AB} = 8$ Hz, 1-H, 8-H and 2-H, 7-H), 1.94 (s, 9-H, 10-H), 2.57 (d, $J = 16$ Hz, 11-H, 22-H), 2.87—3.09 (m, 6 external H), 3.21 (br. s, 4-H, 5-H), 4.50 (~dd, $J_1 = 16$ Hz, $J_2 \approx 10$ Hz, 12-H, 21-H), 4.78 (m, 15-H, 18-H).

This spectrum is remarkable for the following reasons: The signals cannot be divided between "aromatic" and "olefinic" protons; instead, the signals of all the inner protons are shifted to higher field strength and those of the external protons are shifted to lower field strength. This observation, which indicates a diamagnetic ring current in the macrocyclic system, is particularly clearly shown when a comparison is made with the corresponding ^{1}H-NMR absorptions of the precursor *(4)* that is not cyclically conjugated (see Fig. 1)[7].

The opposite shifts of the signals of the neighboring proton pairs 11-H, 22-H and 12-H, 21-H in, respectively, the α- and the β-positions to the phenanthrene unit are striking; even more so is the large shift of the signals of 4-H, 5-H to higher field strength beyond those of all the external protons, including those of the "olefinic" part of the molecule, whereas in phenanthrenes, including the macrocyclic *(1)*[2], it is precisely these protons that normally absorb at lowest field strength.

Because of the importance of this finding the assignment of the two 2H singlets at $\tau = 1.94$ and 3.21 to 9-H, 10-H and 4-H, 5-H, respectively, was checked by synthesis of a molecule *(2)* deuteriated at the 9,10-positions: 4,4'-dimethyltolane was catalytically ($Pd/BaSO_4$ + pyridine, ethyl acetate) deuteriated to α,β-dideuteriostilbene; photochemical cyclodehydrogenation afforded 9,10-dideuterio-3,6-dimethylphenanthrene, which was converted by the reaction series given above into a species *(2)* selectively deuteriated at positions 9 and 10. With this compound the signal at $\tau = 1.94$ did not occur; the signal at $\tau = 3.21$ can therefore be assigned unequivocally to 4-H, 5-H.

Dibenzo[*ab*,*de*]cyclooctadecene *(5)* differs from *(2)* in that the *m*-linkage of the benzene rings prevents complete cyclic conjugation around the macrocyclic system. The synthesis of *(5)* from 3,3'-dimethylbiphenyl *via* 3,3'-bis(1-hexen-5-ynyl)biphenyl was effected analogously to that of *(2)*. *(5)*[4] formed dark red crystals (m. p. 160 °C, dec.) that are extremely sensitive to air. Its ^{1}H-NMR spectrum (CS_2, 100 MHz) is in accordance with an aromatic and an olefinic part in the molecule. In particular, with *(5)* the absorption of the two inner aromatic protons, which correspond to 4-H, 5-H in *(2)*, occurs at the lowest field strength ($\tau = 1.56$). Since the geometrical relations within the 18-membered rings of *(2)* and *(5)* are similar, it must thence be concluded



(5)

[1] Conjugation in Macrocyclic Bonding Systems, Part 21.—Part 20: *H. A. Staab, F. Graf, K. Doerner* and *A. Nissen*, Chem. Ber. *104*, 1159 (1971).

[2] *H. A. Staab, H. Bräunling*, and *K. Schneider*, Chem. Ber. *101*, 879 (1968).

[3] For ease of discussion of their ^{1}H-NMR spectra the C atoms of the phenanthrene portions of *(2)* and *(4)* are numbered as is usual in phenanthrenes.

[4] Correct elemental analyses and molecular weights were obtained for these compounds; the spectroscopic data accord with the structures assumed.

[5] *F. Bohlmann* and *R. Miethe*, Chem. Ber. *100*, 3861 (1967).

[6] We thank Dr. *W. Brügel*, BASF Ludwigshafen, for recording this spectrum.

[7] In this comparison it must, nevertheless, be remembered that in *(4)*, 12-H,21-H and, to a smaller extent, also 4-H, 5-H are under the deshielding influence of the anisotropy of the diacetylene group, although this shifts these signals by no more than 0.5 ppm to lower field strength, as shown by the comparison with the spectrum of *(3)*.

that the strong shielding of 4-H, 5-H in *(2)* cannot be the result of local anisotropic effects of the double bonds. If the induction of a diamagnetic ring current is taken as the criterion of aromaticity, it follows that the macrocyclic system in *(2)*, unlike those in *(1)* and *(5)*, exhibits annulenoid aromaticity. Comparison with the very much stronger shielding of the inner protons in the monocyclic [18]annulene shows, however, that the annulene character of *(2)* is substantially weakened by fusion with the phenanthrene system and that there is here a borderline case between benzenoid and non-benzenoid aromaticity.

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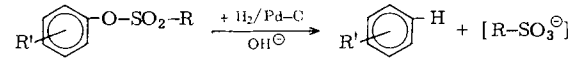
Hydrogenative Removal of Phenolic Hydroxyl Groups

By *Karl Clauss* and *Harald Jensen*[*]

Dedicated to Professor Werner Schultheis on his 70th birthday

The hetero ring of 1,2,3-benzoxathiazin-4(3*H*)-one 2,2-dioxide opens between oxygen and carbon on catalytic hydrogenation with palladium-charcoal in the presence of an equivalent amount of base[1]. Application of this finding to aryl sulfonates *(1)* showed that phenolic hydroxyl groups in general, in the form of their sulfonic esters, can be removed by catalytic hydrogenation at 20—40 °C and atmospheric pressure.



(1)

Bases such as sodium hydroxide solution, alkali-metal alkoxides or tertiary amines accelerate the reaction appreciably, equivalent amounts of the base favoring smooth reaction. Suitable solvents are water and, in particular, methanol. It is advisable to choose a temperature between 20 and 40 °C so as to prevent over-hydrogenation. Palladium on charcoal is a suitable catalyst; platinum and nickel catalysts do not have comparable activity. Contrary to the case of the known fission of aryl sulfonates by an excess of Raney nickel[2–5], catalytic amounts of palladium suffice in our reaction (1.0—1.5 mg of Pd per mmol of ester).

Examples of this hydrogenolysis are collected in Tables 1—3.

Chloro substituents are removed by the hydrogenation, so that a correspondingly larger amount of base must be added to bind the liberated hydrogen chloride. Groups such as formyl, susceptible to hydrogenation, are hydrogenated, so that the otherwise difficultly accessible 3-methoxybenzyl alcohol can be obtained from vanillin in this way.

Table 1. Hydrogenative cleavage of phenyl esters C_6H_5—O—SO_2R to benzene (palladium-charcoal as catalyst).

R	Solvent	Base	Yield [%]
H_2N	H_2O	NaOH	50
H_2N	CH_3OH	CH_3ONa	65
CH_3	CH_3OH	CH_3ONa	75
CH_3	CH_3OH	Et_3N	82
CH_3O—CONH	CH_3OH	CH_3ONa	90
C_6H_5—CONH [a]	H_2O	NaOH	70

[a] The chloride of this acid was synthesized from benzoic acid and chlorosulfonyl isocyanate according to [6].

Table 2. Hydrogenative cleavage of aryl methanesulfonates (palladium-charcoal in methanol, triethylamine as base).

Aryl	Product	Yield [%]
1-Naphthyl	Naphthalene	72
2-Naphthyl	Naphthalene	91
3-Methoxyphenyl	Anisole	65
4-Methoxyphenyl	Anisole	72
3-Chlorophenyl	Benzene	90
4-Chlorophenyl	Benzene	85
4-Formyl-2-methoxyphenyl	3-Methoxybenzyl alcohol	70

Table 3. Hydrogenative cleavage of aryl *N*-(methoxycarbonyl)amidosulfates [a] to benzene (palladium-charcoal in methanol, sodium methoxide as base).

Aryl	H_2 [mol]	Base [mol]	Yield [%]
Phenyl	1	1	90
4-Chlorophenyl	2	2	82
2,4,6-Trichlorophenyl	4	4	55

[a] Prepared by addition of methanol to aryloxysulfonyl isocyanates [7].

Experimental:

The phenol is esterified with methanesulfonyl chloride in the presence of the equivalent amount of pyridine at 20 to 60 °C. For the hydrogenation, this aryl sulfonate (60 mmol) in methanol (100 ml) is stirred with triethylamine (60 mmol) and 1.5 g of catalyst (containing 5 % palladium on charcoal) under hydrogen at 25—40 °C until the calculated amount of hydrogen has been consumed. The catalyst is filtered off and the cleavage product is isolated (benzene was not isolated but was determined by gas chromatography).

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[2] *G. W. Kenner* and *M. A. Murray*, J. Chem. Soc. *1949*, S 178.

[3] *S. Mitsui* and *S. Imaizumi*, J. Chem. Soc. Jap., Pure Chem. Sect. *79*, 1436 (1958); Chem. Zbl. *1959*, 17036.

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[6] *R. Graf*, Angew. Chem. *80*, 179 (1968); Angew. Chem. internat. Edit. *7*, 172 (1968).

[7] *G. Lohaus*, Chem. Ber. *105*, 2791 (1972).

Simple Synthesis of Carbonyl Chloride Fluoride and Carbonyl Bromide Fluoride

By *Günter Siegemund*[*]

Dedicated to Professor Werner Schultheis on the occasion of his 70th birthday

The methods reported previously for preparation of carbonyl chloride fluoride and carbonyl bromide fluoride

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require use of halogen fluorides or hydrogen fluoride or, in the latter case, application of pressure. In addition, these syntheses[1-3] lead to mixtures of carbonyl halide fluorides of various compositions.

We have found that the catalyzed reaction of carbon tetrachloride with sulfur trioxide[4], leading to phosgene, can be applied also to chlorofluoro- and bromofluoromethane, thus providing a convenient route to COFCl and COFBr requiring only the use of conventional glass apparatus.

Reaction of SO_3 with trichlorofluoromethane in the presence of mercury salts or sulfuric acid, even at room temperature, affords only carbonyl chloride fluoride and sulfuryl chloride or polysulfuric chlorides.

$$CFCl_3 + SO_3 \xrightarrow[\text{or } H_2SO_4]{Hg^{I}/Hg^{II}} COFCl + ClSO_2(SO_3)_nCl$$

The COFCl contains as only impurity the $CFCl_3$ that is carried over with it, and the two are readily separated by distillation.

Tribromofluoromethane[5] and SO_2 afford carbonyl bromide fluoride, sulfur dioxide and bromine in a homogeneous reaction in the absence of catalysts.

$$CFBr_3 + SO_3 \rightarrow COFBr + SO_2 + Br_2$$

Here too COF_2 cannot be detected on gas chromatography. Of the by-products, bromine can be removed by addition to trichloroethylene, and sulfur dioxide by a wasteful distillation although it is rarely a disturbing ingredient.

Carbonyl difluoride can also be prepared by this method, namely by treating CF_2Br_2 with SO_3.

Carbonyl chloride fluoride:

65% oleum (600 g) is placed in a 1-l three-necked flask fitted with a thermometer, dropping funnel whose tube dips into the liquid, and two Dimroth condensers one above the other (+10 °C, −30 °C), and to it $CFCl_3$ (275 g, 2 mol) is added at 28—34 °C during 5 h. The gas evolved is passed through a condenser and a H_2SO_4 wash bottle into a cold trap (−78 °C), where a mixture (138 g; CO_2 3%, $CFCl_3$ 23%, COFCl 74% ≙ 60% yield) condenses. SO_3 (470 g, 5.87 mol) containing 1 g each of Hg_2SO_4 and $HgSO_4$ was treated in a similar apparatus with $CFCl_3$ (227 g, 1.66 mol) during 3 h, the temperature rising to 61 °C. The product condensed in the cold trap (142 g) was fractionated by distillation at a low temperature [yield 114 g ≙ 83% of COFCL, b. p. −45° to −40 °C ([1]: −42 °C]).

Carbonyl bromide fluoride:

SO_3 (200 g, 2.5 mol) was placed in a 500-ml three-necked flask fitted with a thermometer, dropping funnel, magnetic stirrer and two condensers one above the other (+10 °C, 0 °C) and was treated with $CFBr_3$ (135 g, 0.5 mol) during 2 h at 37—43 °C. To remove the bromine, the product was passed, before condensation, through a wash bottle containing $CHCl{=}CCl_2$ irradiated by UV light. The trap content (80 g) afforded a mixture (60 g), b. p. −17.5 to −10 °C, of CO_2 3%, SO_2 29.5% and COFBr 67.5% ≈ 64% yield.

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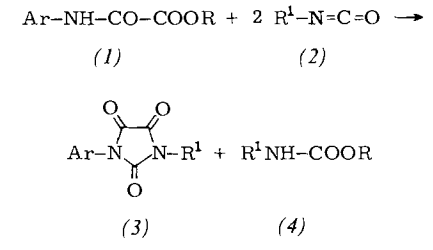
Reactions of *N*-Aryloxamidic Esters with Isocyanates[1]

By *Kurt Kraft* and *Johannes Reese*[*]

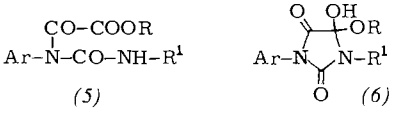
Dedicated to Professor Werner Schultheis on his 70th birthday

We have obtained the 1,3-disubstituted 2,4,5-imidazolidinetriones *(3)* by base-catalyzed reaction of *N*-aryloxamidic esters *(1)* (R = CH_3, C_2H_5 or C_4H_9) with isocyanates *(2)*. Triethylamine, tributylamine and 1,4-diazabicyclo-[2.2.2]octane are particularly good catalysts. The alcohol



(1) *(2)* *(3)* *(4)*

ROH liberated reacts with the isocyanate to give the urethane *(4)*. The expected urea derivatives *(5)* could not be detected even after reaction under the mildest conditions, and this indicates formation of semiacetals *(6)* as unstable intermediates.



(5) *(6)*

Table 1. 1,3-Disubstituted 2,4,5-imidazolidinetriones *(3)*.

Ar	R^1	M.p. [°C]	Yield [%]
C_6H_5	n-C_8H_{17}	67	65
4-C_6H_5—N=N—C_6H_4	n-C_8H_{17}	152	68
C_6H_5	c-C_6H_{11}	149	67
4-NO_2—C_6H_4	C_6H_5	209	72
4-CH_3O—C_6H_4	C_6H_5	136	78
3-Cl—C_6H_4	C_6H_5	183	84
3-CF_3—C_6H_4	C_6H_5	193	69
4-C_6H_5—N=N—C_6H_4	C_6H_5	200	98
2-Pyridyl	C_6H_5	163	91
4-$(CH_3)_2N$—C_6H_4	3-Cl—C_6H_4	124	95
4-Cl—C_6H_4	3-Cl—C_6H_4	224	89
4-CH_3CO—C_6H_4	3-Cl—C_6H_4	212	67
9,10-Dioxo-9,10-dihydro-2-anthryl	3-Cl—C_6H_4	269	96
4-CH_3SO_2-3-Cl—C_6H_3	4-Cl—C_6H_4	251	96
1-Naphthyl	4-Cl—C_6H_4	248	81
3-CF_3—C_6H_4	3,4-Cl_2—C_6H_3	231	89

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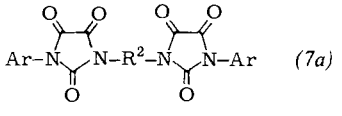
The substituents on *(3)* can be varied over a wide range (Table 1). Reactive isocyanates afford *(3)* in an exothermic reaction even at 10—20 °C. *N*-Alkyl- and *N*-cycloalkyloxamidic esters do not afford compounds *(3)* under the conditions described.

If the reactants and solvents are chosen suitably the compounds *(3)* and *(4)* can be separated without difficulty. The possible choice of reactants is increased because compounds *(3)* with aromatic R^1 can be formed either from ArNH—CO—COOR and R^1NCO or from R^1NH—CO—COOR and ArNCO. When R^1 is aliphatic or cycloaliphatic, separation is easy because of large differences in the solubility of *(3)* and *(4)*.

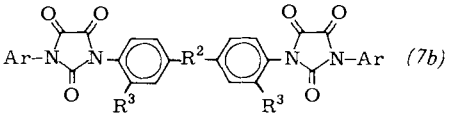
Table 2. Bis(3-aryl-2,4,5-trioxo-1-imidazolidinyl)arenes *(7a)* and *(7b)*.

Ar	—R^2— [a]	R^3	M.p. [°C]	Yield [%]
(7a)				
3-Cl—C_6H_4	—1,3-C_6H_4—		318—320	94
3-Cl—C_6H_4	—1,4-C_6H_4—		360	95
(7b)				
C_6H_5	—	CH_3	315	90
C_6H_5	—CH_2—	H	276	86
C_6H_5	—O—	H	282—284	91
C_6H_5	—SO_2—	H	360	85
3-Cl—C_6H_4	—	H_3CO	312—314	82
3-Cl—C_6H_4	—	H	360	90
3-Cl—C_6H_4	—CH_2—	H	272	94
3-Cl—C_6H_4	—1,4-O—C_6H_4—O—	H	316	80
2-Cl—C_6H_4	—CH_2—	H	256	65
3,4-Cl_2—C_6H_3	—O—	H	295—297	92

[a] Dashes (—) in this column denote valence bonds; the compounds are biphenyl derivatives.



(7a)



(7b)

The hitherto unknown compounds *(7)* with two 2,4,5-imidazolidinetrione rings can be synthesized by the same method (Table 2)[1]. This class of compound is characterized by high melting points and low solubility. Their preparation is particularly easy in dimethylformamide, dimethylacetamide or 1-methylpyrrolidone. Poly-2,4,5-imidazolidinetriones can be obtained by treating diisocyanates with *N,N'*-arylenedioxamidic esters[2] and are characterized by high thermal stability, elasticity and surface hardness.

1,3-Diphenyl-2,4,5-imidazolidinetrione:

Ethyl *N*-phenyloxamidate (193 g, 1 mol) and phenyl isocyanate (238 g, 2 mol) in anhydrous benzene (1000 ml) are stirred together at 25 °C and treated with triethylamine (3 ml) with good cooling. The temperature rises to about 50 °C. After boiling for 1 h under reflux the mixture is diluted with light petroleum (700 ml) and cooled to 15 °C. The crystalline product is filtered off, washed with ligroin and dried at 100 °C in a vacuum: yield 231 g (87 %); m.p. 204 °C ([3]: 204 °C). Only ethyl phenylcarbamidate (m.p. 52 °C) and further amounts of the trioxo compound can be isolated from the mother liquors. Both compounds were identified by mixed melting points and IR spectra.

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[1] *J. Reese* and *K. Kraft*, DOS 1916932 (1969), Reichhold-Albert-Chemie.

[2] *G. Schade* and *W. Blaschke*, DOS 1770146 (1968), Dynamit Nobel; *J. Reese* and *K. Kraft*, DOS 1920845 (1969), 2030233 (1970), and 2139005 (1971), all Reichhold-Albert-Chemie.

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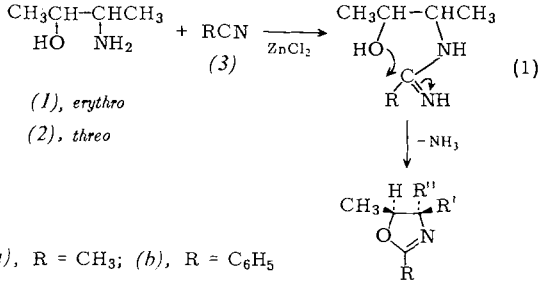
Stereochemistry of the 2-Oxazoline Synthesis from β-Amino Alcohols and Nitriles

By *Ronald A. Wohl*[*]

Witte and *Seeliger* recently reported a convenient synthesis of 2-oxazolines from β-amino alcohols and nitriles in the presence of a Lewis acid catalyst such as zinc acetate or zinc chloride[1,2]. In connection with other work on 2-oxazolines[3] we were interested in establishing the stereochemistry of this reaction.

erythro-3-Amino-2-butanol *(1)* on reaction with acetonitrile or benzonitrile in the presence of $ZnCl_2$ gave the *cis*-2-oxazolines, *(4a)* and *(4b)*, exclusively. *threo*-3-Amino-2-butanol *(2)* similarly afforded the corresponding *trans*-2-oxazolines, *(5a)* and *(5b)*, exclusively. The purity of the products was established by IR and NMR spectra and GC analysis and based upon comparison with authentic samples[3]. In agreement with the observed retention of configuration, the mechanism of the above reaction therefore may be formulated as shown in eq. (1).



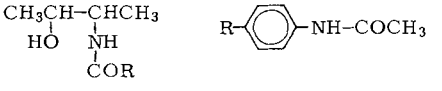
(1)

(1), erythro
(2), threo

(a), R = CH_3; *(b)*, R = C_6H_5

(4), R' = CH_3, R'' = H
(5), R' = H, R'' = CH_3

We attempted to substitute amides for the nitriles: *threo*-3-amino-2-butanol *(2)* on reaction with acetamide or benzamide in the presence of 0.04 eq. of $ZnCl_2$ gave the corresponding *trans*-2-oxazolines, *(5a)* and *(5b)*, in good yield. The reaction here proceeds presumably *via* the intermediate amide *(6)*. *erythro*-3-Amino-2-butanol, on the other hand, under the above conditions did not give any of the *cis*-oxazolines *(4)*, but the reaction stopped at the amide stage *(6)*.



(6a), R = CH_3 *(7a)*, R = H
(6b), R = C_6H_5 *(7b)*, R = CH_3

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This discrepancy in the behavior of the *erythro* and *threo* amino alcohols, *(1)* and *(2)*, reflects the increased steric strain of ring closure to give the *cis*-2-oxazolines *(4)* which possess two vicinal eclipsed methyl groups. The widely different ease of cyclization of *N*-(2-hydroxyalkyl) amides to 2-oxazolines has been noted repeatedly[2].

Because $ZnCl_2$ seemed to catalyze the *N*-acylation of the starting amino alcohols *(1)* and *(2)* with acetamide to give *(6a)* we investigated the reactions of aniline and *p*-toluidine with acetamide to yield the corresponding amides *(7a)* and *(7b)* and ammonia. $ZnCl_2$ showed a pronounced catalytic effect in this reaction, *i.e.* acetamide is a much superior acetylating reagent in the presence of $ZnCl_2$. BF_3 has been reported to have a similar effect[4].

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[2] For a recent review on 2-oxazoline chemistry see: *J. A. Frump*, Chem. Rev. *71*, 483 (1971).

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Stereospecific Attack of Nucleophilic Reagents on Nitrooxirane Sugars

By *Satoru Kumazawa*, *Tohru Sakakibara*, *Rokuro Sudoh*, and *Toshio Nakagawa*[*]

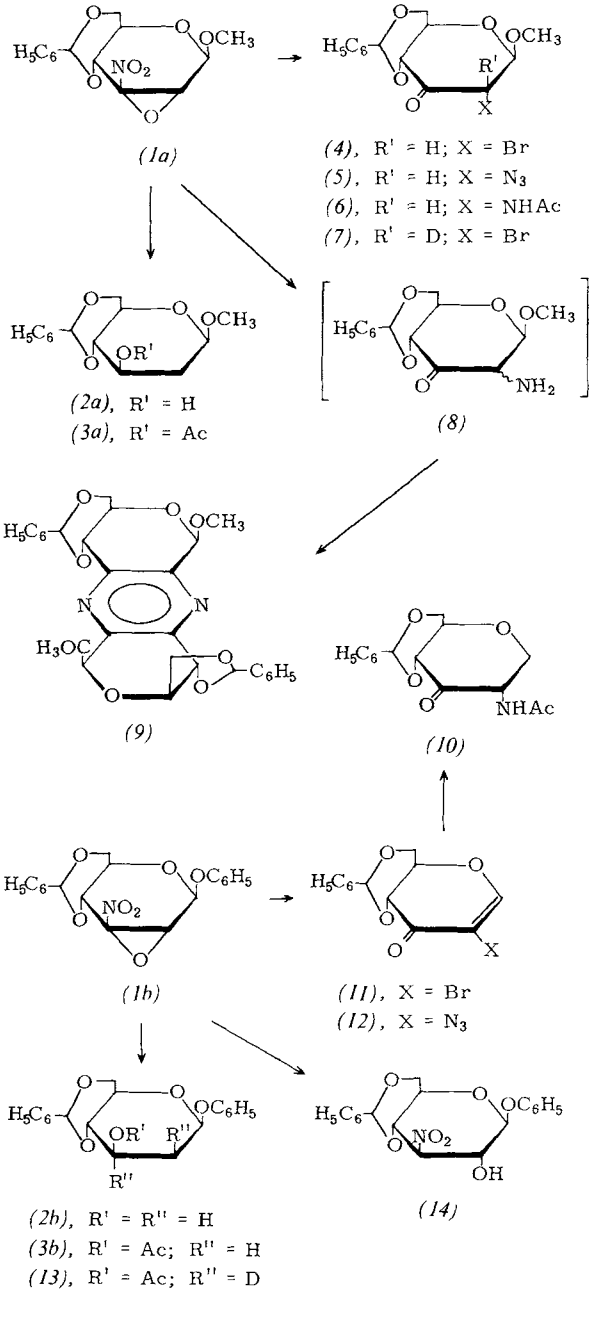
Newman and *Angier*[1] succeeded in synthesizing nitrooxiranes (α-nitro epoxides) which enter into reaction with nucleophilic compounds. Shortly thereafter we[2] and also *Baer* and *Rank*[3] prepared some "nitrooxirane sugars". We have now found that reaction of the new sugar derivatives with nucleophiles is not only smooth but also highly stereospecific, involving denitration and fission of the epoxide ring, so that these derivatives should be useful intermediates.

Hydrogenation of methyl *(1a)* and phenyl 2,3-anhydro-4,6-*O*-benzylidene-3-*C*-nitro-β-D-allopyranoside *(1b)*[4] by $LiAlH_4$ (in THF, 2 h at room temperature) leads almost quantitatively to the 2-deoxyglucosides *(2a)* and *(2b)*, respectively[5], which were isolated and characterized as the 3-*O*-acetates *(3a)* [m.p. 141—142 °C (from ethanol); $[\alpha]_D = -69.3°$ ($CHCl_3$, $c = 1.00$); ^{1}H-NMR ($CDCl_3$): $\tau = 8.00$ (3H/s, equat. *O*-Ac[6]), $J_{2^a,3} = 11$ Hz, $J_{3,4} = 9$ Hz] and *(3b)* [m.p. 136—137 °C (from ethanol); $[\alpha]_D = -65.6°$ ($CHCl_3$, $c = 1.00$); ^{1}H-NMR ($CDCl_3$): $\tau = 7.96$ (3H/s, equat. *O*-Ac[6]), $J_{2^a,3} = 11$ Hz, $J_{3,4} = 9$ Hz]. After catalytic hydrogenation of *(1b)* over Pd/C or Raney Ni in ethyl acetate only the 3-deoxy-3-nitroglucoside *(14)*[4] was isolated (over 85% yield).

On treating *(1a)* with lithium bromide (monohydrate, excess in THF at room temperature) we obtained, in 75% yield, methyl 4,6-*O*-benzylidene-2-bromo-2-deoxy-β-D-*ribo*-3-hexulopyranoside *(4)* [m.p. 210—212 °C (dec.; from ethanol); $[\alpha]_D = -131°$ ($CHCl_3$, $c = 1.00$); ^{1}H-NMR (D_6-DMSO): $\tau = 5.15$ (d, 1-H), $J_{1,2} = 9$ Hz; IR (KBr): $\nu_{C=O} = 1728\ cm^{-1}$ (equat. α-bromo ketone[7])]. With lithium azide, *(1a)* gave the unstable 2-azide analog *(5)*, which, after hydrogenation with Pd/C in dioxane/acetic anhydride, was isolated and characterized as the 2-acetamide *(6)* [m.p. = 204—205 °C (dec.; from acetone/ethanol); $[\alpha]_D = -49.8°$ (DMSO, $c = 1.00$); ^{1}H-NMR (D_6-DMSO): $\tau = 5.28$ (d, 1-H), $J_{1,2} = 8.5$ Hz] in 83% yield based on *(1a)*.

An interesting result was that the phenyl analog *(1b)* with lithium bromide gave, not the corresponding 2-bromoglycoside, but only (77% yield) the 2-bromo compound *(11)* [m.p. = 174—175 °C (dec.; from ethanol); $[\alpha]_D = +213°$ ($CHCl_3$, $c = 1.00$); ^{1}H-NMR (D_6-DMSO): $\tau = 1.85$ (s, 1-H)] with β-elimination of phenol. The again unstable 2-azido compound *(12)* was obtained in over 76% yield by use of sodium azide; this could be characterized by hydrogenation to the 2-acetamide *(10)* [m.p. 242 °C (dec.; from ethanol); $[\alpha]_D = -55.5°$ (DMSO, $c = 1.00$); ^{1}H-NMR (D_6-DMSO); $\tau = 5.79$ (dd, 1^a-H) and 6.48 (dd, 1^e-H), $J_{1^a,1^e} = 10.5$ Hz, $J_{1^a,2} = 8$ Hz, $J_{1^e,2} = 2$ Hz].

On treating *(1a)* with concentrated methanolic ammonia we obtained the pentacyclic compound *(9)* in 78% yield



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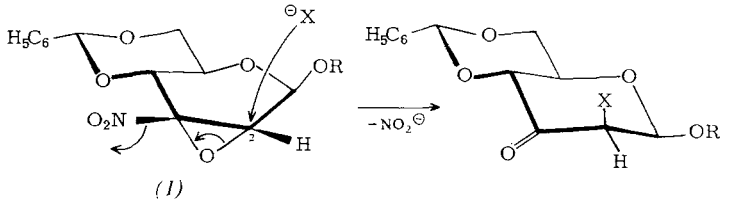
[m. p. = 248—250 °C (dec.; from methanol); $[\alpha]_D = -129°$ (DMSO, $c = 1.00$); ^{1}H-NMR (D_6-DMSO); $\tau = 4.13$ and 4.18 (s, 1-H + 1'-H and s, 2 α-benzyl-H, or *vice versa*); MS: 520 (M^+)]. The amino ketone *(8)* is probably first formed, being later aromatized by dimerization and air oxidation to yield *(9)*.

The first step in this nucleophilic denitration and ring opening of *(1a)* and *(1b)* can be interpreted as S_N2'-like attack by the nucleophiles H^-, D^-, Br^-, N_3^- and $:NH_3$ on C-2.

In the reaction with $LiAlH_4$ the ulose first formed is hydrogenated to the compound *(2)* having an equatorial hydroxyl group[8], this reaction course being proved by reduction of *(1b)* with $LiAlD_4$ and subsequent acetylation by acetic anhydride in pyridine to afford the homogeneous [2^a,3-D_2]-2-deoxyglucoside *(13)* in more than 75% yield; the [2^e,3-D_2]-epimer could not be detected by NMR spectroscopy.



(1)

(a), R = CH_3; *(b)*, R = C_6H_5

From the two following experiments it can be concluded that in the conversion of *(1a)* into *(4)* the attack of the bromide ion is not S_N1-like but S_N2'-like and that because of the Δ2-effect[9] the unstable 2^a-bromo ulose is at once isomerized irreversibly to the 2^e-bromo isomer *(4)*: 1. Treating *(1a)* with anhydrous lithium bromide in D_2O-THF afforded the 2^e-bromo-2^a-deuterio compound *(7)* as almost sole product. 2. *Only* the starting material *(4)* could be recovered from a solution of *(4)* in D_2O-THF containing lithium bromide and nitrite. It is probable that *(1a)* is converted into *(5)* analogously.

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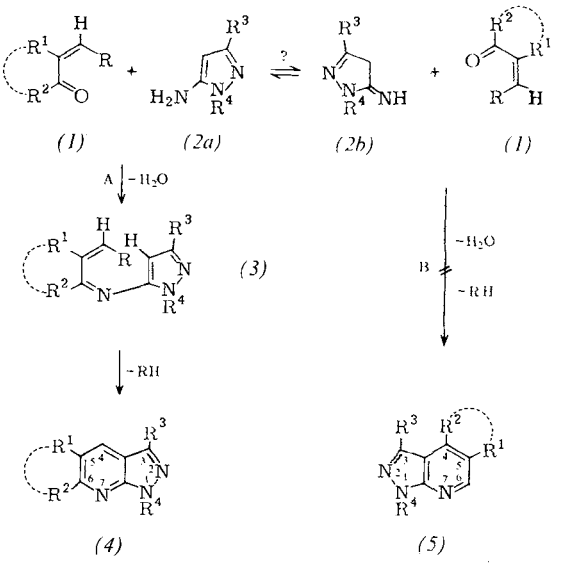
A New Variant for the Synthesis of 1*H*-Pyrazolo[3,4-*b*]pyridines[**]

By *Jochen Häufel* and *Eberhard Breitmaier*[*]

A generally applicable method for the synthesis of 1*H*-pyrazolo[3,4-*b*]pyridines *(4)* involves the cyclocondensation of 1,3-dicarbonyl compounds with 5-aminopyrazoles *(2)* in glacial acetic acid[1]. We have found that the 1,3-dicarbonyl compounds may be replaced by 2-(hydroxymethylene)cycloalkanones, 2-alkyl-3-alkoxy- or 2-alkyl-3-amino-acroleins *(1)*, R = OH, OR', or NH_2. Such condensations make it possible to prepare numerous 1*H*-pyrazolo[3,4-*b*]pyridines *(4)* that were not previously accessible (Table 1).



(1) *(2a)* *(2b)* *(1)*

(3)

(4) *(5)*

R = OH, OR', NH_2

Ring closure to *(4)* can occur in two ways (A and B), according to whether the 5-aminopyrazole reacts as the enamine *(2a)* or the imine *(2b)*. The decision between the two routes A and B can be made only with compounds *(1)* where $R^2 \neq H$.

Table 1. Examples of new 1*H*-pyrazolo[3,4-*b*]pyridines *(4)* [a].

R^1	R^2	R^3	R^4	Variant	Yield [%]	M. p. [°C] B. p. [°C/torr]
$-(CH_2)_4-$		CH_3	C_6H_5	A	70	86
$-(CH_2)_4-$		H	C_6H_5	A	65	103
$-(CH_2)_4-$		H	C_2H_5	C	54	101/0.1
$-(CH_2)_5-$		CH_3	C_6H_5	—	56	118
$-(CH_2)_5-$		CH_3	CH_3	B	80	104
$-(CH_2)_6-$		CH_3	C_6H_5	—	52	117
$-(CH_2)_{10}-$		CH_3	C_6H_5	A	65	95
CH_3	H	CH_3	C_6H_5	A	75	92
CH_3	H	H	C_6H_5	B	78	122
CH_3	H	CH_3	CH_3	B	67	78
CH_3	H	H	C_2H_5	C	62	55/0.1
n-C_3H_7	H	H	C_2H_5	C	87	84/0.05
n-C_4H_9	H	CH_3	C_6H_5	B	57	33
n-C_4H_9	H	H	C_2H_5	C	51	110/0.9

[a] Mass spectra, ^{13}C-NMR, ^{1}H-NMR and UV spectra of all the compounds accord with the structures assigned.

With 3-alkoxy-2-alkyl- or 2-alkyl-3-amino-acroleins *(1)*, R^1 = alkyl, R^2 = H, both routes lead to the same products. However, 2-(hydroxymethylene)cycloalkanones *(1)*, R = OH, $R^1-R^2 = -(CH_2)_n-$, would yield the 5,6-cycloalkeno compound *(4)* by route A or the 4,5-cycloalkeno isomer *(5)* by route B. In fact, the reaction proceeds by route A as can be shown both chemically and spectroscopically. In the absence of glacial acetic acid the 2-(hydroxymethylene)cycloalkanones *(1)*, $R^1-R^2 = -(CH_2)_n-$, react to give isolable Schiff bases *(3)*, whose structure can be proved by their mass, IR and ^{1}H- and ^{13}C-NMR

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spectra. If these products *(3)* are heated in glacial acetic acid, they afford 5,6-cycloalkeno-1*H*-pyrazolo[3,4-*b*]pyridines *(4)* whose structures follow especially from their ^{13}C chemical shifts and the $^{13}C—^{1}H$ coupling constants of the carbon atoms of the pyridine ring: the unsubstituted carbon atom C-4 of the 5,6-cycloalkeno-1*H*-pyrazolo[3,4-*b*]pyridines obtained appears as a doublet at $\delta \approx -128$ ppm with a coupling constant $J_{CH} \approx 155-160$ Hz. These values accord with the δ and J_{CH} data found for C-4 of pyridines[2], in contrast to $\delta \approx -145$ to -150 ppm and $J_{CH} \approx 150$ to 175 Hz found for C-2 of pyridines.

1H-Pyrazolo[3,4-b]pyridines (4)

Compounds *(1)* (0.02 mol) and *(2)* (0.02 mol) are heated together under reflux in glacial acetic acid for 24 h. If the product *(4)* does not crystallize on cooling, isolation is achieved by variant A, B or C below.

Variant A: The reaction mixture is treated cautiously with water. The precipitate is collected and recrystallized from ethanol/water. *Variant B:* The reaction mixture is treated with sodium hydroxide solution until alkaline. The oil that separates is extracted with ether. After removal of the ether in a rotary evaporator the residue is recrystallized from ethanol/water. *Variant C:* The acetic acid is distilled off and the oil is distilled at *ca.* 0.1–0.9 torr.

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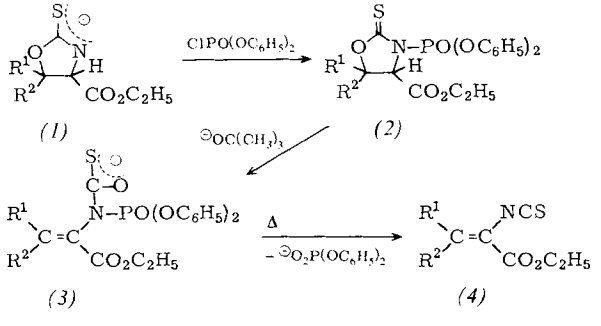
3-Substituted 2-Isothiocyanatoacrylic Esters[**]

By *Dieter Hoppe*[*]

Dedicated to Professor Hans Brockmann on the occasion of his 70th birthday

2-Isothiocyanatoacrylic esters *(4)*, hitherto unknown, can be conveniently prepared in a single-flask synthesis if oxazolidine-2-thione anions *(1)* (prepared by basic condensation of ethyl isothiocyanatoacetate with carbonyl compounds[1]) are phosphorylated by diphenyl phosphorochloridate at 20—30 °C in tetrahydrofuran and the resulting ethyl 3-(diphenoxyphosphoryl)-2-thioxooxazolidine-4-carboxylates *(2)* are then ring-opened by potassium *tert*-butoxide to *N*-phosphoryl-*N*-vinylthiocarbamates *(3)*[2],



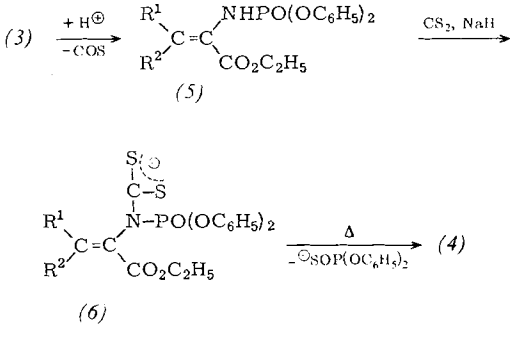
which fragment to *(4)* and diphenyl phosphate (variant A) (Table 1).

Table 1. Ethyl 2-isothiocyanatoacrylates *(4)* synthesized.

(4) R^1	R^2	Variant	Yield [a] [%]	M. p. [°C]
(a) CH_3	CH_3	A [b]	67	34—35
(b) —$(CH_2)_5$—		A [b]	65	—
(c) —$(CH_2)_4$—		A [b]	63	32—33
(d) $(CH_3)_2CH$	H	B [b]	60	—
(e) C_6H_5	H	B [c]	51	30—31
(f) C_6H_5—CH=CH	H	B [c]	54 [d]	75—83
(g) C_6H_5	CH_3	B [c]	56 [e]	—

[a] Based on ethyl isothiocyanatoacetate.
[b] Extraction by *n*-pentane, see text.
[c] Extraction by cyclohexane, see text.
[d] Mixture of isomers.
[e] *E*/*Z* ratio 1.5:1.

3-Aryl-substituted and 3-monosubstituted acrylic esters *(4)* sensitive to alkoxides cannot be prepared in this way, or at most in unsatisfactory yields. This complication can be avoided by variant B, according to which *(3)* is first converted into a 2-(diphenoxyphosphorylamino)acrylic ester *(5)* by glacial acetic acid at -60 °C, which is then allowed to react with carbon disulfide and sodium hydride, affording an *N*-phosphoryldithiocarbamate *(6)* which decomposes at 20—40 °C to *(4)* and *O,O'*-diphenyl thiophosphate[3] (Table 1).



Starting from the diastereoisomeric anions *(1)* only one isomer of the (3-monosubstituted) esters *(4d)* and *(4e)* is obtained, which on the basis of their NMR spectra presumably have the *Z*-configuration. For comparison, *(4a)* was also prepared, in 80% yield, by sulfuration of ethyl 2-isocyano-3,3-dimethylacrylate[4] [—NC in place of —NCS in *(4a)*] by 2-methyl-2-propanethiol and azobisisobutyronitrile[5].

The structures of the compounds *(4)* are proved by their IR, NMR, and UV spectra and by their CH analyses. The IR absorptions of the isothiocyanato groups (2020—2050 cm^{-1}) and the ester carbonyl groups (1720 cm^{-1}) are shifted towards long wavelengths in comparison with those of saturated 2-isothiocyanatoalkanoic esters.

The intermediates *(2c)* [m.p. 89 °C; IR: 1735 (C=O), 1580 (OC_6H_5), and 1320 cm^{-1} (P→O)] and *(5e)* [m.p. 112 °C; IR: 3150 (NH), 1715 (C=O), 1625 (C=C), and 1585 cm^{-1} (OC_6H_5)] were isolated and characterized.

In 2-isothiocyanatoacrylates *(4)* the NCS group undergoing ready attack by nucleophiles is attached to a C=C double bond which is capable of ring closure. Hence the esters *(4)* can serve as starting materials for synthesis of thiazole derivatives.

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2-Isothiocyanatoacrylic esters

To a solution of *(1)* (40 mmol; prepared by use of sodium hydride[11]) are added dry tetrahydrofuran (30 ml) at 20 °C and, instead of glacial acetic acid[11], diphenyl phosphorochloridate (10.8 g, 40 mmol), the mixture then being stirred for a further 30 min at 20—30 °C. Next potassium *tert*-butoxide (5.6 g, 50 mmol) in tetrahydrofuran (50 ml) is added dropwise at −60 °C and after 15 min a sample is warmed to 20 °C and examined by IR spectroscopy. If intense absorption at 2050 cm^{-1} is observed, the mixture is warmed to 20 °C and worked up *(variant A)*. In other cases *(variant B)* the mixture is neutralized by glacial acetic acid (3.0 g) at −60 °C and freed from solvent in a vacuum (bath temp. max. 40 °C). A solution of the residue in benzene (200 ml) is clarified by neutral silica gel (8 g), and the solvent is removed in a vacuum. The residual *(5)* is dissolved in tetrahydrofuran (50—100 ml) and carbon disulfide (10 ml) and added dropwise to a stirred suspension of finely powdered sodium hydride (1.1 g, 44 mmol) in tetrahydrofuran (20 ml) at 20—40 °C, and the whole is left to react for a further 3 h at 30—40 °C under N_2. For working up, the solvent is removed in a vacuum (bath temp. max. 40 °C), the residue is stirred with light petroleum (b.p. 40—60 °C)/ether (2:1) (150 ml) and set aside for 1 h at 0 °C. The solution is decanted or sucked free from undissolved material (caution: contains NaH). The filtrate is evaporated in a vacuum and the residue is extracted with 100 ml of *n*-pentane or cyclohexane (see Table 1). After at least 8 h standing at 0—5 °C the solution is separated from undissolved material and on evaporation of the solvent affords a 50—70% yield of *ca.* 95% pure *(4)*. For complete purification of *(4)* this product is chromatographed over neutral silica gel in a column cooled with ice-water and eluted with peroxide-free ether/*n*-pentane (1:2) (R_F = 0.5—0.6). Readily volatile esters *(4)* (mol. wt. <200) withstand distillation at 0.1 torr (bath temp. <70 °C).

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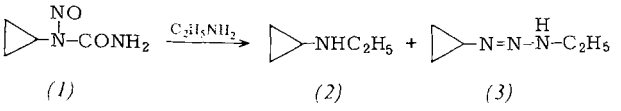
Azo Coupling by Cyclopropanediazonium Ions

By *Wolfgang Kirmse, William J. Baron*, and *Ulrich Seipp*[*]

Azo coupling of aromatic diazonium salts plays an important part in the synthesis of intermediates and of dyes[1], whereas aliphatic diazonium salts almost always react with elimination of nitrogen[2]. We report here the ability of cyclopropanediazonium ions to undergo azo coupling.

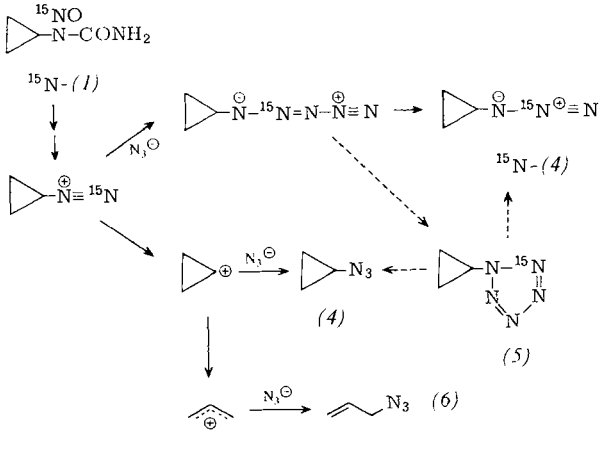
Alkaline fission of nitrosoacylamines leads to diazonium ions and/or diazo compounds in a sequence of several steps[3]. By treatment of *N*-cyclopropyl-*N*-nitrosourea *(1)*[4] with ethylamine/methanol (molar ratio 2:1) at −8 °C we obtained cyclopropyl methyl ether (12%), *N*-ethylcyclopropylamine *(2)* (8%), and 1-cyclopropyl-3-ethyltriazene *(3)* (30%). The triazene *(3)* [IR: 3435 (NH), 3085, 3010, 1020 (cyclopropane), 1503 cm^{-1} (N=N); NMR: δ = 6.9 (s, br. 1H), 3.37 (q, 2H), 3.1 (m, 1H), 1.15 (t, 3H), 0.73 (m, 4H)] agreed in all its properties with a sample prepared by a known triazene synthesis[5] from cyclopropyl azide[4] and ethylmagnesium bromide.



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

A triazene was also obtained from *(1)* and dimethylamine, but in poorer yield (*ca.* 5%) and lower purity. However, isobutanediazonium ions and methanediazonium ions gave no triazene under corresponding conditions but only substitution products.

Treatment of *(1)* with lithium azide in methanol afforded cyclopropyl azide *(4)* as the main product[4]. Use of ^{15}N-labeled *(1)* (96% of ^{15}N) led to a sample of *(4)* that according to its mass spectrum contained 68% of ^{15}N. This accords with the intensity ratio of the azide bands of labeled (2054 cm^{-1} in CCl_4) and unlabeled *(4)* (2107 cm^{-1}). The frequency difference indicates labeling at N-2 of the azide group: for terminally labeled *p*-toluenesulfonyl azide $\Delta\nu_{N_3}$ has been found to be −19 cm^{-1} and for the non-terminally labeled azide −41 cm^{-1}[6]. Cyclopropanediazonium ions thus react with azide ions for the most part by a pentazene mechanism. Whether unlabeled *(4)* is formed by way of a pentazole *(5)*[7] or by "direct" substitution must remain open for the time being; experiments at 0 and 25 °C showed no difference in the ^{15}N content of *(4)*, and below 0 °C the reaction was very slow. Simultaneous formation of small amounts of allyl azide *(6)* (*ca.* 6%) shows that decomposition of cyclopropanediazonium ions competes with azo coupling even in the presence of azide.



Under the above reaction conditions ^{15}N-labeled *N*-butyl-*N*-nitrosourea gave 1-butyl azide not containing ^{15}N. The observed differences in reactivity suggest that cyclopropanediazonium ions occupy a position between the purely aliphatic and the aromatic diazonium ions.

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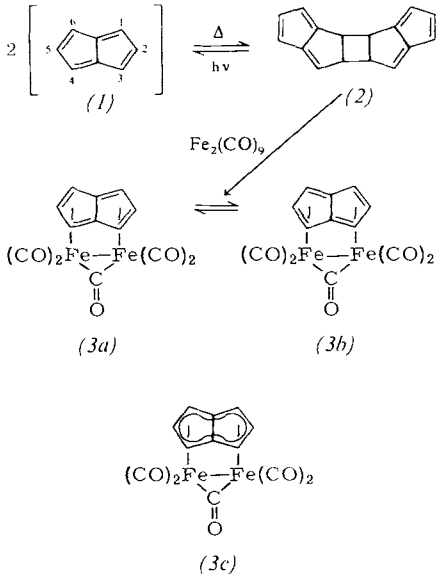
Synthesis of Carbonyliron Complexes of Pentalene and Its Derivatives

By *Wolf Weidemüller* and *Klaus Hafner*[*]

Pentalene *(1)* and its methyl derivatives are characterized—like cyclobutadiene[1]—by a highly pronounced tendency to dimerization[2, 3]. The only alkyl derivative hitherto isolated, 1,3,5-tri-*tert*-butylpentalene, is, for steric reasons, not capable of dimerization[4]. On photolysis in a matrix at −196 °C several dimeric pentalenes could be converted to the corresponding, UV-spectroscopically detectable monomers.



We have now observed that fission of pentalene dimers is also achieved by transition metals. Treating *(2)*[5] with $Fe_2(CO)_9$ at 50 °C (in methylcyclohexane under carbon monoxide in a sealed vessel) yielded the pentalene-pentacarbonyldiiron complex *(3)* as yellow-brownish crystals, stable at room temperature under nitrogen[6] [yield 9%, m. p. 140 °C dec., 100 MHz ^{1}H-NMR spectrum (in C_6D_6): A_2B system at $\tau = 4.54$ (t, $J = 2.5$ Hz, H-2, H-5) and $\tau = 6.77$ (d, $J = 2.5$, H-1, H-3, H-4, H-6); IR spectrum (KBr pellet): 2030, 1985, 1945 cm^{-1} (terminal CO), 1750 cm^{-1} (bridging CO)]. Similarly the corresponding complex of 1,3-dimethylpentalene could be synthesized in 21% yield from its dimer[3] as green crystals, melting at 136 °C [100 MHz ^{1}H-NMR spectrum (in C_6D_6): A_2B system at $\tau = 5.61$ (t, $J = 2.5$ Hz, H-5) and $\tau = 6.93$ (d, $J = 2.5$ Hz, H-4, H-6); $\tau = 6.00$ (s, H-2) and $\tau = 8.87$ (s, $2CH_3$); IR spectrum (KBr pellet): 2020, 1980, 1940 cm^{-1} (terminal CO), 1750 cm^{-1} (bridging CO)]. Like the IR spectra the mass spectra of these complexes too resemble those of the 1-dimethylamino and 1-phenyl derivatives[8] of *(3)* obtained from the corresponding 1,2-dihydropentalenes[7] and $Fe(CO)_5$. Besides molecular ion peaks ($M^+ = 354$ and 382) fragment peaks due to successive cleavage of five carbonyl groups and two iron atoms also appear.

The NMR spectra of these complexes do not allow distinction of either structures *(3a)*⇌*(3b)* with rapidly oscillating π-electron system or *(3c)* with a delocalized pentalene ligand. *F. G. A. Stone et al.*[9] recently reported the comparable bis(trimethylgermyldicarbonylruthenium) complex obtained by dehydrogenative transannular cyclization of cyclooctatetraene. Its bonding structure proposed on the basis of an X-ray analysis is not incompatible with a structure of type *(3c)*.

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Synthesis of 4-Mercapto-2-azetidinones having α-Isopropylideneacetate Groups on Nitrogen

By *Rudolf Lattrell*[*]

Dedicated to Professor Werner Schultheis on the occasion of his 70th birthday

4-Mercapto-2-azetidinones (4-mercapto-β-lactams) having α-isopropylideneacetate groups attached to the nitrogen have not hitherto been described although they have long been discussed in connection with degradation reactions of penicillins and biosynthesis of penicillins and cephalosporins[1]. We have now found a general method for the synthesis of 4-mercapto-2-azetidinones[2], and in particular for compounds of type *(5)* named in the title.

Starting materials were the *cis*- or *trans*-4-tritylthio-2-azetidinones *(2)* that have been obtained from the cysteine derivative *(1)* and substituted acetyl chlorides. Methanethiol can be split from the primary products of the β-lactam syntheses under mild conditions[2, 3].

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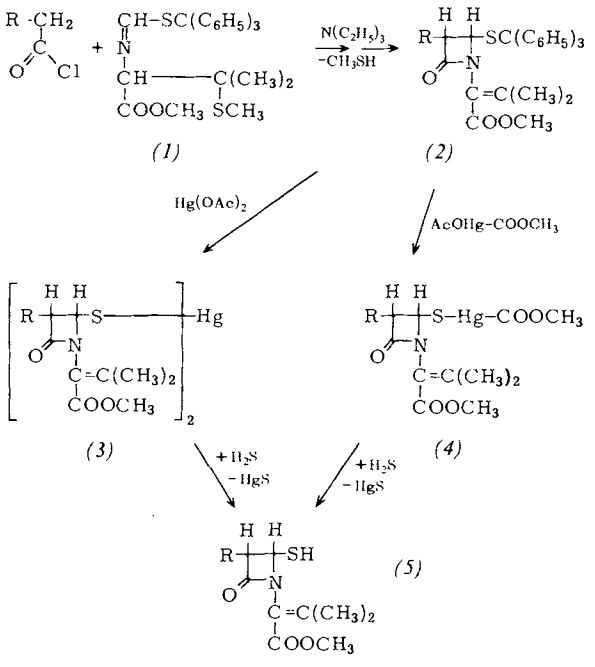
The (tritylthio)azetidinones *(2)* react with mercury(II) acetate or (methoxycarbonyl)mercury acetate in methanol at room temperature to give good yields of the (mercurithio)-azetidinones of type *(3)* or *(4)*, respectively. These relatively apolar compounds can be purified without decomposition by chromatography on silica gel.

The products *(3)* and *(4)* react instantaneously with hydrogen sulfide in an inert solvent, even in the cold, with deposition of mercury sulfide and quantitative formation of the relatively stable 4-mercapto-2-azetidinones *(5)*.



The structures of the compounds *(5)* (Table 1) was proved by IR [3.9 μm (SH), 5.6 μm (lactam-CO)] and NMR spectra (the SH-proton appears as a doublet with $J = 8$ Hz in the region $\delta = 2$ ppm) and, for the crystalline compounds, also by elemental analysis.

Table 1. Mercaptoazetidinones *(5)* prepared from *(2)* by way of *(3)* or *(4)*.

	R	*(5)* Configuration	*(5)* Yield [%]	*(5)* M.p. [°C]	*(3)* or *(4)* M.p. [°C]	*(3)* or *(4)* Yield [%]
a	N_3	*cis*	100	Oil	*(3)* amorphous	70
b	N_3	*trans*	100	Oil	*(3)* amorphous	68
c	phthal-imido	*cis*	80	160—162	*(3)* 228 (dec.)	80
d	phthal-imido	*trans*	98	155—156	*(4)* 180 (dec.)	96
e	phenyl-acetamido	*cis*	100	105—107	*(4)* amorphous	83

Methyl cis-2-[2-(methoxycarbonyl)mercurithio-4-oxo-3-(phenylacetamido)-1-azetidinyl)-3-methylcrotonate (4e)

cis-(2e)[3] (2.95 g, 5 mmol) and (methoxycarbonyl)mercury acetate[4] (3.2 g, 10 mmol) are stirred together in methanol (50 ml) and methylene chloride (10 ml) for 2 h at room temperature. After working up with water and methylene chloride, the oily residue from the organic phase is chromatographed over silica gel (Woelm, 0.02—0.5 mm, deactivated with 10% of water; column 2.5 × 110 cm) with ethyl acetate/cyclohexane (2:1). *(4e)*, $R_F = 0.19$, is eluted as an amorphous foam (yield 2.5 g, 83%).

Methyl cis-2-[2-mercapto-4-oxo-3-(phenylacetamido)-1-azetidinyl]-3-methylcrotonate (5e)

A slow stream of hydrogen sulfide is passed for 4 h through a solution of *(4e)* (0.6 g, 1 mmol) in methylene chloride (10 ml) at 0 °C. After filtration from the precipitated mercury sulfide the solvent is removed in a vacuum. The resinous residue (0.36 g, quantitative yield) is pure *(5e)*. Dissolution in benzene and cooling to 10 °C affords colorless crystals of m.p. 105—107 °C.

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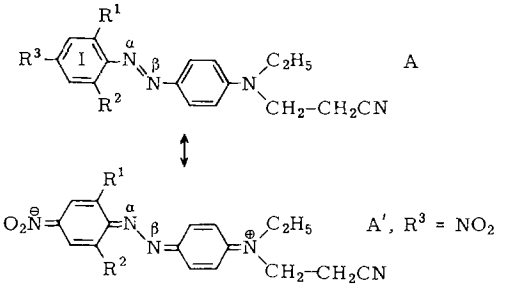
Steric Hindrance in Strongly Polar 2,6-Disubstituted Azobenzenes

By *Ernst Hoyer*, *Rudolf Schickfluss*, and *Willi Steckelberg*[*]

Dedicated to Professor Werner Schultheis on the occasion of his 70th birthday

Azobenzenes of type A are of industrial interest as dispersion dyes for polyester fibers since by substitution at positions 2, 4 and 6 of ring I colors can be obtained ranging from yellow to violet. To clarify the relations between structure and color, the substituents R^1, R^2 and R^3 were varied systematically and the absorption spectra of the dyes *(1)—(33)* obtained were measured in the region of the long-wave π-π* bands that determine the shade and depth of color of the compounds.



It is known that *trans*-azobenzene is planar[1] and that substituents at position 2 to the azo bridge exert steric hindrance that can lead to twisting of the substituted benzene ring in relation to the —N=N— bond[2—5]. However, those investigations relate mainly to slightly polar azobenzenes symmetrically substituted by methyl groups and halogen atoms and do not permit unequivocal relation of steric hindrance to the position of the π-π* bands.

We have found that in strongly polar compounds of type A, $R^3 = NO_2$, these bands are particularly strongly influenced by steric hindrance if R^1 and R^2 are halogen or tetrahedral substituents. The bands are shifted to shorter wavelength by an unusually large amount and their intensity decreases [Table 1, *(1)–(9)*].

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However, even if only one of the substituents R^1 and R^2 is a "planar" group ($-NO_2$, carbonyl function), then a pronounced steric effect on the azobenzene group appears to be prevented because these substituents relinquish their coplanarity with the phenyl nucleus I in order to avoid hindrance by the azo bridge [*(1)*, *(10)–(14)*].

This explanation is supported by the observation that with such substituents the bathochromic influence at position 4 to the azo group is greater than at position 2 [*(18)*, *(27)–(29)*, *(1)*] while in the case of spherical or tetrahedral substituents it is almost equal at positions 2 and 4 [*(18)–(26)*].

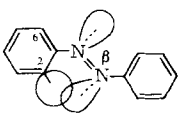
Steric effects are not brought about by substitution with nitrile groups. The hypsochromic shift in 2,6-substituted azobenzenes is considerably reduced when there is no nitro group at position 4 (R^3) [compare *(18)*, *(21)*, *(33)* with *(1)*, *(4)*, *(5)*].

Table 1. Absorption (λ_{max}) and extinction maxima (ε) of the π-π^* bands of azobenzenes of formula A (in methanol). The compounds which were purified by column chromatography and recrystallization were homogeneous on thin-layer chromatography and afforded correct elemental analyses.

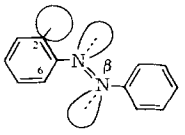
Cpd.	R^1	R^2	R^3	λ_{max} [nm]	ε
(1) [a]	H	H	NO_2	453	44000
(2)	CH_3	H	NO_2	454	42000
(3)	CH_3	CH_3	NO_2	383	24000
(4)	Cl	H	NO_2	475	40000
(5)	Cl	Cl	NO_2	417	31000
(6)	CF_3	H	NO_2	480	44000
(7)	CF_3	Br	NO_2	423	26000
(8)	SO_2CH_3	H	NO_2	500	35000
(9)	SO_2CH_3	Br	NO_2	433	30000
(10)	COC_6H_5	H	NO_2	482	40000
(11)	COC_6H_5	Br	NO_2	503	41000
(12)	NO_2	H	NO_2	491	38000
(13)	NO_2	Br	NO_2	498	34000
(14)	NO_2	NO_2	NO_2	520	48000
(15)	CN	H	NO_2	504	45000
(16)	CN	CN	NO_2	549	38000
(17)	CN	Br	NO_2	506	37000
(18) [a]	H	H	H	399	40000
(19)	CH_3	H	H	402	18000
(20)	H	H	CH_3	399	53000
(21)	Cl	H	H	412	37000
(22)	H	H	Cl	409	42000
(23)	CF_3	H	H	416	34000
(24)	H	H	CF_3	416	41000
(25)	$SO_2C_2H_5$	H	H	429	45000
(26)	H	H	$SO_2C_2H_5$	430	40000
(27)	COC_6H_5	H	H	419	36000
(28)	H	H	COC_6H_5	432	43000
(29)	NO_2	H	H	425	36000
(30)	CN	H	H	434	42000
(31)	H	H	CN	433	45000
(32)	NO_2	NO_2	H	450	27000
(33)	Cl	Cl	H	396	22000

[a] *Bridgeman* and *Peters* [8] obtained the same results from measurements in ethanol.

As shown in Table 1, steric hindrance is strikingly evident in the position of λ_{max} when (i) R^1 and R^2 are bulky substituents and (ii) a strongly polar azobenzene system capable of mesomerism is involved. A qualitative explanation has been given previously[6] for similar relations in the stilbene steries.



B



C

A planar *trans*-azobenzene with one substituent on C-2 can assume conformation B or C, that of C being sterically more favorable than that of B. Thus stronger steric hindrance is to be expected only when C-2 and C-6 of one benzene ring are both substituted so that one substituent necessarily overlaps the sp^2 electrons of the β-nitrogen atom. In strongly polar azobenzenes of type A, $R^3 = NO_2$, quinonoid structures such as A′ contribute more to the mesomerism than in less polar azobenzenes and this leads to shortening of the distance between the substituent and the β-nitrogen atom.

Since A′ is more strongly involved in the excited state than in the ground state[6, 7] the steric hindrance is greater in the excited than in the ground state and a short-wave shift of the π-π^* bands is always produced.

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Hydrogenation of a Substituted Glutarodinitrile

By *I. Leupold* and *H.-J. Arpe*[*]

Dedicated to Professor Werner Schultheis on the occasion of his 70th birthday

Suitably substituted diamines with at least four C atoms between the amino groups are desirable starting materials for preparation of transparent polyamides by condensation with dicarboxylic acids. Economic access to them is provided by dinitriles since these can be hydrogenated to diamines by use of cobalt catalysts and a large excess of NH_3. By-products are obtained owing to loss of ammonia, *e. g.* pyrrolidines and piperidines from the parent succinodinitriles and glutarodinitriles, respectively[1, 2].

Thus on catalytic hydrogenation of 2-(1-cyclohexenyl)-3,3-pentamethyleneglutarodinitrile *(1)*, the diamine *(3)* and the piperidine derivative *(4)* are both obtained, but in addition the partially hydrogenated amino nitrile *(2)* can also be isolated. Any one of the products *(2)*, *(3)* and *(4)* containing an irreducible double bond can be made to preponderate by choice of reaction conditions (see Experimental).

The primary nitrile group is more easily hydrogenated than the secondary one, so that, with simultaneous migration of the double bond into conjugation, 2-cyclohexylidene-3,3-pentamethylene-5-aminovaleronitrile *(2)*, m. p. 148 °C, can be obtained under mild conditions of hydrogenation. Since cyclization to 1-(1-cyclohexenyl)-3-azaspiro[5.5]undecane *(4)*, m. p. 50 °C, is hindered by the bulky cyclohexane rings, 2-(1-cyclohexenyl)-3,3-pentamethylene-1,5-pentanediamine *(3)*, m. p. 59 °C, is formed preferentially below 150 °C, the double bond migrating back to its original position. At higher temperatures *(4)* is the main product. This reaction opens an easy route to a 3-azaspiro[5.5]undecane.

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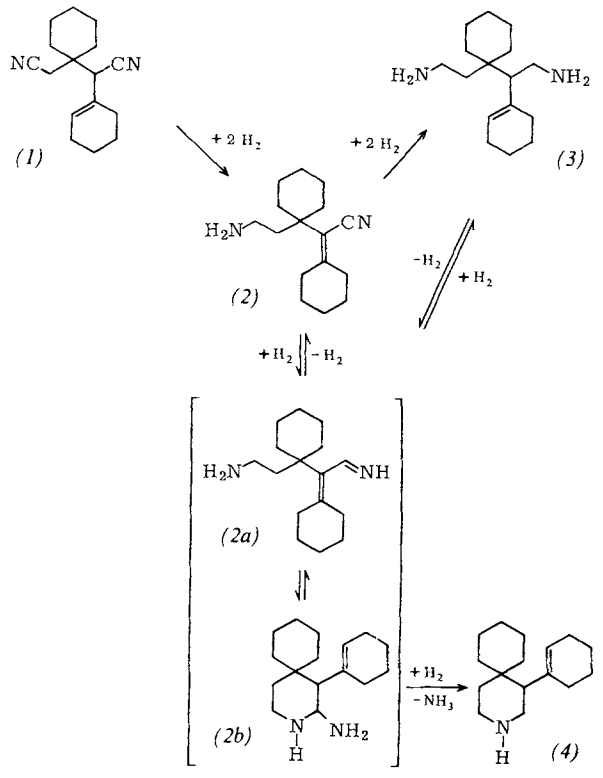

The formation of *(4)* probably occurs by intramolecular amine-imine addition and hydrogenative deamination by way of the unisolated intermediates *(2a)* and *(2b)*. This is indicated also by smooth reaction to give the piperidine *(4)* when the individual compounds *(2)* and *(3)* are hydrogenated at about 200 °C.

Experimental

(1)[3] (60 g) is shaken in a 1-l V4A autoclave with a hydrogenation catalyst (5 g), containing 39 wt.-% of cobalt as well as SiO_2, at a hydrogen pressure of 200 atm for 24 h, with the tabulated results.

T [°C]	Solvent [g]	Yields [mol-%] (2)	(3)	(4)
100	150 Dioxane, 75 NH_3	61	35	2
130	100 NH_3	10	75	6
200	150 Dioxane	< 1	< 1	97

Separation of the products was by chromatography with ethanol/conc. NH_3 (4:1) on silica gel. The products are eluted in the order *(2)*, *(4)*, *(3)*. The structures assigned accord with C, H, N and ^{1}H-NMR, IR and MS data.

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Removal of Allyl groups by Formic Acid Catalyzed by (Triphenylphosphane)palladium

By *H. Hey* and *H.-J. Arpe*[*]

Dedicated to Professor Werner Schultheis on the occasion of his 70th birthday

In the presence of (triphenylphosphane)palladium catalysts, allyl phenyl ether and allyl carboxylates react with carboxylic acids by exchange of the allyl group for the acidic H of the acid[1, 2].

$$C_6H_5O\text{—Allyl} + R'COOH \xrightarrow{Cat.} C_6H_5OH + R'COO\text{—Allyl}$$

$$RCOO\text{—Allyl} + R'COOH \xrightarrow{Cat.} RCOOH + R'COO\text{—Allyl}$$

However, in an attempt to obtain allyl formate in this way from allyl acetate and formic acid, the starting materials decomposed to acetic acid, CO_2 and propene.

$$CH_3COO\text{—Allyl} + HCOOH \xrightarrow{Cat.} CH_3COOH + CO_2 + H\text{-Allyl}$$

This reaction can be applied also to other allylic and substituted allylic compounds (Table 1).

Table 1. Examples of the removal of allyl groups by formic acid. Typical experiment: A solution of palladium acetate (112 mg, 0.5 mmol) and triphenylphosphane (1.572 g, 6.0 mmol) in allyl acetate (75 g, 0.75 mol) was treated under argon with formic acid (11.5 g, 0.25 mol) and warmed to 90 °C. Rapid evolution of gas began at 70 °C and was complete within 1 h. The solution contained, besides catalyst and unchanged allyl acetate, 0.24 mol of acetic acid, and the gas contained 48 vol.-% of CO_2, 50 vol.-% of propene and 1 vol.-% of H_2 (from decomposition of formic acid).

Starting materials Allyl cpd.	[mol]	HCOOH [mol]	Liquid products	[mol]	Gaseous products [a] olefin [vol.-%]	CO_2	H_2
allyl propionate	0.4	0.05	propionic acid	0.05	propene 49	51	
allyl phenyl ether	0.36	0.05	phenol	0.04	propene 47	52	
methallyl acetate	0.41	0.05	acetic acid	0.05	isobutene 48	52	
2-butenyl acetate	0.4	0.05	acetic acid	0.05	1-butene 34, *trans*-2-butene 7, *cis*-2-butene 2.5	56	
cinnamyl acetate	0.2	0.2	acetic acid 1-phenylpropene 3-phenylpropene	0.1 0.08 0.02		74	26 [b]
triallylamine	0.49	0.05	diallylamine, allylamine and other products		propene 17	50	32 [b]

[a] Measured in a sample of the gas.
[b] Formed by decomposition of formic acid.

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Catalysts that can be used with triphenylphosphane, in place of palladium acetate, are bis(pentanedionato)palladium, palladium chloride, bis(benzonitrile)palladium chloride and tetrakis(triphenylphosphane)palladium; also a combination of tributylphosphane and palladium acetate. The molar ratio Pd:P should be at least 1:4 to prevent separation of palladium.

The reaction of allyl acetate and formic acid occurs differently from the formally similar reduction of, *e.g.*, butyraldehyde[3] and alkenes[4] by formic acid in the presence of transition-metal catalysts. Monodeuteriopropene is obtained on treatment of allyl acetate with DCOOD and CH_3COOH (1:1) but not with HCOOH and CH_3COOD (1:1). We also observed a kinetic isotope effect: At 80 °C in the second experiment deallylation occurred twice as fast as in the first experiment. Thus fission of the C—H bond of formic acid is slow, as well as in the oxidative degradation of formic acid on a Pd^{II}/Cu^{II} catalyst[5].

On incomplete reaction of allyl acetate with formic acid the solution contained about 2% of allyl formate which decomposed rapidly into CO_2 and propene even at 60 °C in presence of (triphenylphosphane)palladium acetate. Cleavage of a substituted allyl formate, 2,7-octadienyl formate, in presence of palladium acetate and dimethylformamide has been described recently[6].

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Simplified Synthesis of Pentafluoro-1-iodoethane and Heptafluoro-2-iodopropane

By *Hans Millauer*[*]

Dedicated to Professor Werner Schultheis on the occasion of his 70th birthday

Perfluorinated alkyl iodides such as pentafluoro-1-iodoethane *(1)* and heptafluoro-2-iodopropane *(2)* are of preparative interest in the laboratory and in industry as, *e.g.*, telogens for preparation of perfluorinated telomers Hitherto they have been prepared mainly by treatment of iodine pentafluoride/iodine mixtures ('IF') with tetrafluoroethylene *(3)* or hexafluoropropene *(4)* by one of various techniques[1]. *(1)* is also formed on reaction of tetrafluoro-1,2-diiodoethane *(5)* or a $CF_2{=}CF_2/I_2$ mixture with hydrogen fluoride and mercury oxide[2] or lead dioxide[3].

We have now found that the iodides *(1)* and *(2)* can be advantageously synthesized by treating the corresponding perfluoroalkene *(3)* or *(4)* and iodine with a readily obtainable, non-metallic oxidizing agent in an excess of hydrogen fluoride. Also, *(5)* may be used in place of *(3)* and iodine. Suitable oxidizing agents are oxo acids of quinque- or hepta-valent halogens (*e.g.* $HClO_3$, HIO_3, H_5IO_6), nitric acid, chlorine and sulfuryl chloride. These reagents have the advantage over oxides of higher-valent metals that they form only volatile reduction products. The reactions with Cl_2 or SO_2Cl_2 occur under anhydrous conditions and are catalyzed by antimony(v) halides. The stoichiometry generally depends on the available number of oxidation equivalents, *e.g.*:

$$7\ CF_2I{-}CF_2I + 7\ HF + H_5IO_6 \xrightarrow[150\ °C]{\text{excess HF}} 7\ CF_3{-}CF_2I + 4\ I_2 + 6\ H_2O$$

Experimental

$CF_2I{-}CF_2I$ *(5)* (177 g, 0.50 mol), periodic acid (17.1 g, 0.075 mol) and hydrogen fluoride (200 g, 10 mol) are heated at 150 °C for 5h in a 1-l autoclave (Hastelloy C) fitted with a push-pull stirrer and electric heating. After cooling to 120 °C the volatile products are allowed to escape slowly, being led first through a wash bottle containing 800 ml of water, then through a second containing 200 ml of 20% KOH (all vessels and connections of PVC) and finally through a drying tower containing granulated $CaCl_2$ into a trap cooled to −78 °C. The condensate (109 g) consists of $CF_3{-}CF_2I$ *(1)* (*ca.* 98 vol.-%) and $CF_2{=}CF_2$ *(3)* (2 vol.-%; gas chromatography).

	Starting materials [mol]		T [°C]	Reaction time [h]	Main product Yield (%) calc. on F cpd.
0.5 *(5)*	0.10 $NaIO_3$		150	5	74 *(1)*
0.5 *(5)*	0.17 HNO_3		155—165	5	84 *(1)*
0.5 *(5)*	0.25 Cl_2		100—130	3	72 *(1)*
0.5 *(5)*	0.27 SO_2Cl_2		160—170	3	77 *(1)*
0.5 *(5)*	0.27 SO_2Cl_2	0.05 $SbCl_5$	160—170	3	94 *(1)*
1.0 *(3)*	0.50 Cl_2	2.35 I_2	160	5	64 *(1)*
0.5 *(4)*	0.17 HNO_3	0.32 I_2	150—160	3	75 *(2)*
0.5 *(4)*	0.28 Cl_2	0.32 I_2 + 0.10 $SbCl_5$	100—140	5	86 *(2)*

The tabulated results were obtained analogously.

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^{1}H-NMR Spectrum of [^{15}N]Pyridine in the Nematic Phase

By *Christian Schumann* and *Roger Price*[*]

Dedicated to Professor Werner Schultheis on the occasion of his 70th birthday

The only method for determining the geometrical structure of molecules in the liquid phase is NMR spectroscopy in liquid-crystalline solvents. It has hitherto been restricted to small molecules[1] with up to ten magnetically active nuclei[2], usually protons. Comparison of the results with those from electron-diffraction, microwave spectroscopy or X-ray analysis has shown that direct dipole-dipole coupling constants between protons generally give correct structural data, whereas for couplings in which other nuclei are involved larger systematic deviations may occur. This has been ascribed to the anisotropy of the indirect coupling constants and to the influence of molecular vibrations on the direct coupling constants.

Since, with the availability of modern techniques, nuclei other than protons are assuming ever increasing importance, we have selected [^{15}N]pyridine for an examination as to whether ^{15}N—^{1}H coupling constants also afford incorrect structural parameters. For this purpose the ^{1}H-NMR spectrum was measured at two concentrations in a 1:1 mixture of $CH_3OC_6H_4CH{=}NC_6H_4OCOPr$ and $C_5H_{11}COOC_6H_4COOC_6H_4OC_2H_5$[3]: HFX-90 and WH-90 apparatus from Bruker was used; Fourier transform technique without stabilization was applied. This technique, together with the larger number and smaller width of the lines, allows a considerably better precision in the measurement of the coupling constants than in earlier determinations on [^{14}N]pyridine[4]. Thus nuclear distances could be calculated with good accuracy in spite of the small values of the ^{15}N—^{1}H coupling constants.

Six anisotropic ^{1}H—^{1}H and three anisotropic ^{1}H—^{15}N coupling constants are obtained (Table 1), so that the positions of the protons and the nitrogen nuclei can be determined independently. The modified[4] program UEANMRITR[5] was used for analysis of the spectra. As indirect coupling constants we used the values reported by *Roberts et al.*[6]. 83 lines of spectrum I were assigned with a standard deviation of 0.42 Hz, and 55 lines of spectrum II (standard deviation 0.20 Hz). Figure 1 shows a comparison of the measured and calculated spectrum I; for the plot the line width was taken to be 6 Hz.

Two orientation parameters and three coordinates were calculated from the six ^{1}H—^{1}H coupling constants by a weighted least-squares procedure[7]. Labeling of nuclei and coordinates is shown in Figure 2; the results are collected in Table 2. The structural parameters agree with the microwave geometry[8] within experimental error.

Three values for the coordinate y_6 can be calculated from the three ^{1}H—^{15}N coupling constants. The values obtained

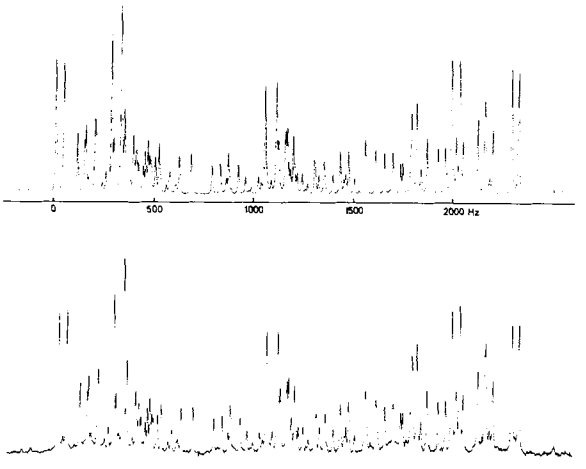

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Fig. 1. Calculated (upper) and experimental ^{1}H-NMR spectrum of [^{15}N]pyridine in the nematic phase.

Table 1. Anisotropic coupling constants [Hz] in [^{15}N]pyridine.

	I (8 wt.-%)		II (4 wt.-%)	
D_{12}	−474.65	±0.08	−484.53	±0.04
D_{13}	− 80.90	±0.19	− 83.75	±0.09
D_{14}	− 38.28	±0.11	− 41.24	±0.06
D_{15}	− 49.87	±0.29	− 55.98	±0.24
D_{23}	−285.13	±0.26	−307.84	±0.13
D_{24}	− 43.58	±0.16	− 49.08	±0.17
D_{16}	39.78	±0.14	44.65	±0.09
D_{26}	15.21	±0.31	15.76	±0.21
D_{36}	12.43	±0.22	12.87	±0.11

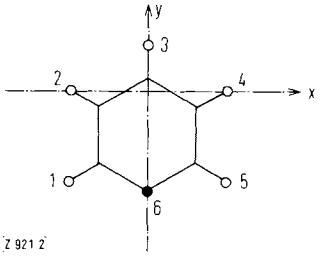

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Fig. 2. Numbering of the nuclei and designation of the coordinates in [^{15}N]pyridine.

Table 2. Structural parameters of pyridine from NMR spectra (I, II) and from microwave spectra.

	I		II		Microwave [8]		
x_1	−2.061	±0.003	−2.062	±0.002	x_1	−2.056	±0.004
y_1	−2.495	±0.008	−2.484	±0.005	y_1	−2.481	±0.004
y_3	1.296	±0.008	1.283	±0.005	y_3	1.288	±0.004
S_{zz}	−0.09058	±0.00004	−0.09465	±0.00003	x_2	−2.153	±0.004 [a]
S_{xx-yy}	−0.03258	±0.00004	−0.02932	±0.00003	y_2	0.0	±0.004 [a]
$y_6(D_{26})$	−2.610	±0.040	−2.609	±0.026	x_3	0.0 [a]	
$y_6(D_{36})$	−2.625	±0.024	−2.602	±0.014	y_6	−2.615	±0.004

[a] These values were kept constant during calculation of the NMR geometry.

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from D_{26} and D_{36} agree with each other and with the microwave values (Table 2). If D_{16} is calculated from this nitrogen position one obtains 40.28 Hz for (I) and 45.23 Hz for (II), *i.e.* a discrepancy of 0.50 and 0.58 Hz, respectively, which, however, can be removed by a vibrational correction[9]. The difference between the harmonic vibrational corrections for the CCH and the CCCCH fragments in benzene[9] (=0.0076 Å) is used for this purpose, with the assumption that the vibrational behavior of the NCH and NCCCH fragments in pyridine is similar. With $\partial D_{16}/\partial r_{16} = 58$ (I) and 62 Hz/Å (II), this affords the corrections 0.44 and 0.47 Hz for the coupling constants D_{16}. These two coupling constants now agree within experimental error with the experimental values.

It can thus be seen that NMR spectra of oriented molecules provide precise geometrical data from coupling constants between nuclei that are separated by three or more bonds, but that vibrational corrections must be applied when the nuclei are closer together, in particular for the directly bonded CH fragment[9]. For $^{19}F—^{19}F$ coupling constants only, a further source of error, namely anisotropy of the indirect coupling constants, seems to be important[10].

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Simple Synthesis of 4-Monosubstituted Arsa- and Phospha-benzenes

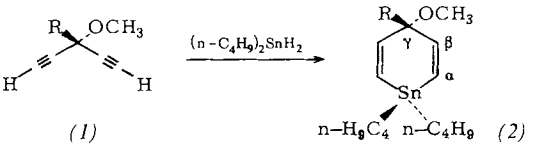
By *Gottfried Märkl* and *Fritz Kneidl*[*]

Dedicated to Professor Werner Schultheis on the occasion of his 70th birthday

Apart from the unsubstituted arsa- and phosphabenzenes[1], only the 2,3,6-tri- and higher aryl-substituted arsabenzenes, prepared by ring expansion of five-membered arsoles, and the 2,4,6-tri- and higher aryl- or alkyl-substituted phosphabenzenes, which are accessible by several routes, have previously been reported[2].

We here report the first preparation of 4-mono-substituted arsa- and phosphabenzenes *(4)* and *(5)* respectively from 4-substituted 4-methoxy-1,4-dihydrostannins *(2)*. These compounds are of particular interest in connection with studies on electrophilic aromatic substitution of arsa- and phosphabenzenes.

Starting materials are the 3-substituted 1,4-pentadiyn-3-ols[3] that are readily accessible from carboxylic esters and Na acetylide; etherification[4] with phase-transfer catalysis affords the 3-methoxy derivatives *(1)* in good yield [*(1a)*, b.p. 84 °C/0.01 torr, yield 78%; *(1b)*, b.p. 86 °C/0.01 torr, yield 87%; *(1c)*, m.p. 36 °C, yield 92%].



(1) *(2)*

a, R = C_6H_5; *b*, R = c-C_6H_{11}; *c*, R = t-C_4H_9

The pentadiynes *(1)* react smoothly with di-*n*-butyltin dihydride in boiling methylcyclohexane containing azoisobutyrodinitrile, cycloaddition affording the 1,4-dihydrostannins *(2)* (see Table 1). The ^{13}C-NMR spectra show conclusively that the six-membered and not the possible, frequently observed[5] five-membered cyclic adducts are formed[6].

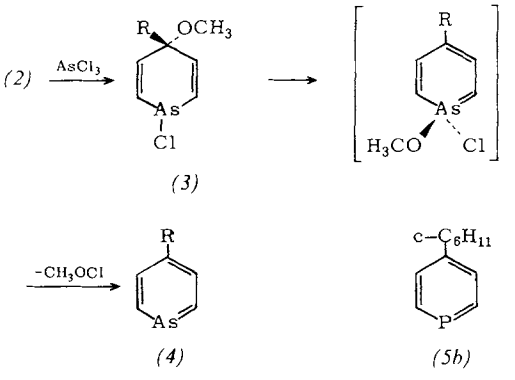
Table 1. Compounds of type *(2)* prepared.

(2a), yield 68%, b.p. 154–158 °C/0.02 torr; *^1H-NMR spectrum* ($CDCl_3$): *n*-C_4H_9: τ = 8.3–9.5 (m), 18 H; OCH_3: 6.65 (s), 3 H; C_6H_5: 2.4–3.0 (m), 5 H; H_α,H_β: 3.6 (s), 3 H, ^{117,119}Sn satellites, $^2J_{Sn-H_\alpha}$ (d) = 57 Hz, $^3J_{Sn-H\beta}$ (d) = 86 Hz, 1 H

(2b), yield 58%, b.p. 160–165 °C/0.02 torr; mol. wt. (osmom.) 415, calc. 412

(2c), yield 61%, b.p. 154–158 °C/0.02 torr; *mass spectrum* (70 eV): M^+ 386, rel. int. 1%; $[M-C_4H_9]^+$ 329, 43%; $[M-2C_4H_9-OCH_3]^+$ 241, base peak; *^{13}C-FT-NMR-spectrum* at 25.2 Hz (Varian XL-100-15, computer 620 i) ($CDCl_3$): $2C_\alpha$, δ = 130.2 (based on i. TMS), $2C_\beta$, 151.2; C_γ, 83.4 ppm; *^1H-NMR-spectrum* ($CDCl_3$): *t*-C_4H_9, *n*-C_4H_9: τ = 8.3–5 (m), 27 H; OCH_3: 6.8 (s), 3 H; H_α, H_β: 3.6 (s), 3 H; ^{117,119}Sn satellites: band complex centered at 4.8 and 2.8, 1 H

The elegant synthesis of boron, phosphorus and arsenic heterocycles by treatment of the tin heterocycles[7–9] with the appropriate halide takes a surprising course with *(2)*: 4-substituted arsabenzenes *(4)* are formed directly from *(2)* and $AsCl_3$ in boiling tetrahydrofuran.



The 1,4-dihydroarsenins *(3)* that occur as intermediates can be detected by NMR spectroscopy on careful working, but they decompose spontaneously, perhaps by way of the 1-chloro-1-methoxyarsabenzenes[10]. The methyl hypochlorite expected as leaving group has an oxidizing action on *(4)*[10]; if this oxidant is trapped with triphenylphosphane[11] (reaction of *(2)* with $AsCl_3$ in the presence of stoichiometric amounts of phosphane), the yield of *(4)* is significantly increased. The arsabenzenes *(4)* are isolated by chromatography on silica gel with *n*-heptane/benzene, forming colorless, distillable, air-sensitive oils; 4-phenylarsenin *(4a)* crystallizes spontaneously (see Table 2).

The arsabenzenes *(4)* exhibit chemical reactivities characteristic of this system: reaction with nucleophiles, *e.g.* phenyllithium, giving dihydroarsenins, and with dienophiles,

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Table 2. Compounds of type *(4)* and *(5)* prepared.

(4a), yield 11.3%, in presence of $(C_6H_5)_3P$, yield 49%, m. p. 51 °C (from ethanol); *mass spectrum* (70 eV): M^+ 216, rel. int. 100%; $[M-As]^+$ 141, 46%; $[M-HCAs]^+$ 34%; *UV spectrum* (ethanol): $\lambda_{max}=302$ ($\varepsilon=31200$), 226 nm (22300); ^{1}*H-NMR spectrum* ($CDCl_3$): C_6H_5: $\tau=2.1$–2.9 (m), 5 H; H_α: 0.2 (d), 2 H, $J=12$ Hz; H_β: 1.9 (d), 2 H, $J=12$ Hz

(4b), yield 29%, in presence of $(C_6H_5)P$, yield 64%, b.p. 107–108 °C/0.02 torr; *mass spectrum* (70 eV): M^+ 222, rel. int. 100%; $[M-CH_3]^+$ 207, 10%; $[M-C_2H_5]^+$ 193, 25%; $[M-C_6H_{12}]^+$ 140, 55%; *UV spectrum* (ethanol): $\lambda_{max}=288$ ($\varepsilon=15900$), 223 nm (13200); ^{1}*H-NMR spectrum* ($CDCl_3$): cyclohexyl: $\tau=7.2$–9.4 (m), 11 H; H_α 0.3 (d), 2 H, $J=11$ Hz; H_β 2.2 (d), 2 H

(4c), yield 52%, molecular distillation; *mass spectrum* (70 eV): M^+ 196, rel. int. 51% $[M-CH_3]^+$ 181, 100%; $[M-C_3H_7]^+$ 153, 17%; *UV spectrum* (ethanol): $\lambda_{max}=275$ ($\varepsilon=15200$), 221 nm (15600); ^{1}*H-NMR spectrum* ($CDCl_3$): *t*-C_4H_9: $\tau=8.8$ (s), 9 H; H_α 0.2 (d), 2 H, $^3J_{H_\alpha,H\beta}=12$ Hz; H_β: 1.9 (d), 2 H

(5b), yield 41%; colorless liquid: *mass spectrum* (70 eV): M^+ 178, rel. int. 10%; $[M-1]^+$ 177, 100%; $[M-C_2H_5]^+$ 150, 10%; $[M-C_3H_7]^+$ 135, 30%; *UV spectrum* (ethanol): $\lambda_{max}=210$ ($\varepsilon=21800$), 225 (14300), 294 (700), 300 nm (560); ^{1}*H-NMR spectrum* ($CDCl_3$): H_α (2d): $\tau=1.30$, 1.47, $^2J_{P,H}=3.6$ Hz; $J_{H_\alpha,H\beta}=11$ Hz, 2 H; H_β (2 d, pseudo-t): 2.1, 2.4, $^3J_{P,H}=9$ Hz, 2 H; cyclohexyl: 7.8–9.2 (m), 11 H

e.g. hexafluorobutyne, acetylenedicarboxylic ester, giving arsabarrelenes[12].

The 4-monosubstituted phosphabenzene *(5b)* (see Table 2) is obtained analogously from *(2b)* and phosphorus tribromide in the presence of triphenylphosphane.

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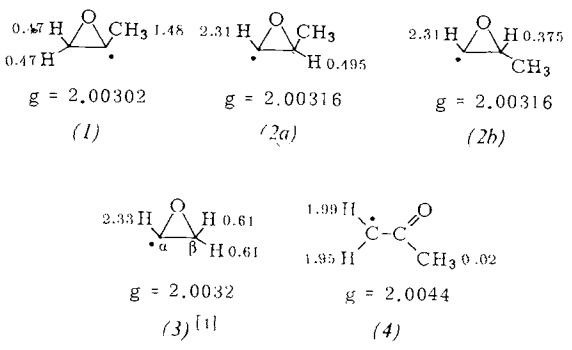
Proof of the Pyramidal Configuration of the Oxiranyl Radical: Two Isomers of the 3-Methyl-2-oxiranyl Radical

By *Günter Behrens* and *Dietrich Schulte-Frohlinde*[*]

If di-*tert*-butyl peroxide in methyloxirane is photolyzed (Philips type SP 1000) between −60 and −30 °C the ESR spectra of three radicals—*(1)*, *(2a)*, and *(2b)*—can be observed (data for hyperfine structure splitting in mTesla).



The unusual coupling constants of the known oxiranyl radical *(3)* have been explained by the assumption of a pyramidal geometry at the C_α atom[11]. Experimental proof of this pyramidal structure has hitherto been lacking because for radical *(3)* only a single form with two magnetically equivalent β-hydrogen atoms is observed.

Our discovery of two isomers *(2a)* and *(2b)* of the 3-methyl-2-oxiranyl radical provides conclusive proof for the occurrence of a pyramidal configuration.

Assuming a pyramidal structure, the observed equivalence of the β-hydrogen atoms of *(1)* and *(3)* can be explained by sufficiently rapid inversion (as for the cyclopropyl radical[12]).

From symmetry reasons the inverted forms of *(1)* and *(3)* have equal energy, whereas *(2a)* and *(2b)* differ energetically. The spectra (Fig. 1) show that *(2b)* occurs somewhat more frequently than *(2a)*.

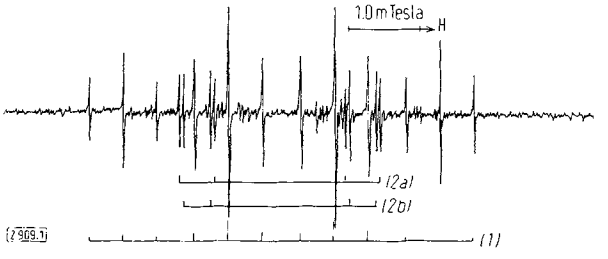


Fig. 1. ESR spectra of the 2-methyl-2-oxiranyl radical *(1)* and the isomeric 3-methyl-2-oxiranyl radicals *(2a)* and *(2b)* obtained on photolysis of 3% of di-*tert*-butyl peroxide in methyloxirane at −40 °C.

A further argument for the pyramidal configuration at C_α of the oxiranyl radical *(3)* is based on the magnitude of the H_α splitting, whose absolute value is shown by our measurements (cf. Table 1) to be greater than that of the methyl radical (−2.304 mT at −177 °C in liquid methane[12]) and must therefore be positive since the H_α coupling of any substituted methyl radical is more positive than that of the methyl radical itself. The large positive splitting proves the strong sp hybridization of the unpaired electron. According to *Fessenden*'s semiempirical relationship[13] from the α-coupling there results an angle of ≈41°

Table 1. Splitting constants of the oxiranyl radical *(3)*.

Solvent	*T* [°C]	a_{H_α} (1) [mTesla]	a_{H_β} (2) [mTesla]	*g*
Water [1]	+20	+2.33	0.61	2.0032
Acetone	−60	+2.43	0.53	2.00320
Ethyl acetate	−70	+2.44	0.52	
Di-*tert*-butyl peroxide	−30	+2.45	0.49	

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between the C—H_α bond and the C—O—C plane, in very good agreement with INDO calculations[1].

The small values of the H_β splittings for *(1)*, *(2)*, and *(3)* can be ascribed to superposition of two coupling mechanisms. Besides the contribution from hyperconjugation, which is positive, there arises, owing to the sp hybridization, an interaction from the π-σ polarization, whose contribution is negative and increases with the s character. This reduces the H_β coupling. Our interpretation is supported by the observed change of the hyperfine structure of the radical *(3)* with the experimental conditions (see Table 1), since an increase of the H_α coupling is connected with a decrease of the H_β splittings.

It is interesting that the acetonyl radical *(4)*[4] occurs during photolysis of di-*tert*-butyl peroxide in methyloxirane above -10 C. This indicates that the oxirane ring of the radical *(1)* opens at these temperatures. Analogous ring opening of *(3)* with formation of the formylmethyl radical cannot be observed under comparable conditions[5].

Received: August 28, 1973 [Z 909 IE]
German version: Angew. Chem. 85, 993 (1973)

[1] *A. J. Dobbs, B. C. Gilbert*, and *R. O. C. Norman*, J. C. S. Perkin II *1972*, 786.

[2] *R. W. Fessenden* and *R. H. Schuler*, J. Chem. Phys. *39*, 2147 (1963).

[3] *R. W. Fessenden*, J. Phys. Chem. *71*, 74 (1967).

[4] *H. Zeldes* and *R. Livingston*, J. Chem. Phys. *45*, 1946 (1966).

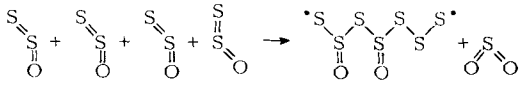
[5] We thank Mr. *H. Niehaus* for technical help with the measurements.

Photoelectron Spectra and Molecular Properties: SSO and OSO[1]

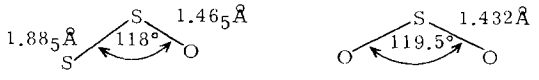
By *Hans Bock, Bahman Solouki, Pavel Rosmus*, and *Ralf Steudel*[*]

Dedicated to Professor Werner Schultheis on the occasion of his 70th birthday

Sulfur burns in oxygen at low pressure to form mixtures of sulfur dioxide and disulfur monoxide[2]. These two triatomic, iso(valence)electronic molecules differ considerably in chemical behavior: thus, in contrast to OSO, SSO polymerizes when its frozen condensate is thawed, or even in the gas phase at partial pressures > 1 torr, by a radical mechanism[3] with partial redox-disproportionation, yielding polysulfur oxides[2]:



The structure of SSO, determined by microwave spectroscopy in gas discharge mixtures ($S+SO_2 \overset{\downarrow}{\rightarrow}$)[2]



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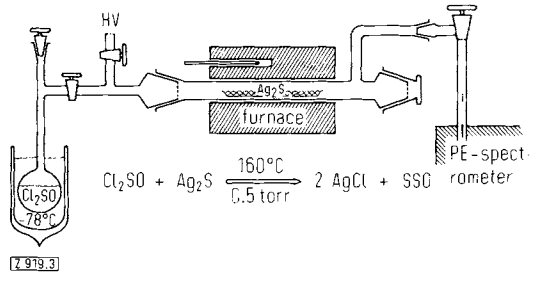
shows a smaller bond angle, and a longer S—O bond than OSO; the S—S bond is relatively short[4]. What are the electronic changes brought about by the replacement O→S?

The photoelectron (PE) spectrum of the stable OSO was published some time ago[5]. For recording that of the unstable SSO it was first necessary to find a method of preparation which, unlike the gas discharge ($S+SO_2 \overset{\downarrow}{\rightarrow}$), would guarantee a steady molecular beam containing more than 75% of SSO for several hours. This was achieved by synthesis from thionyl chloride and silver sulfide[3] directly in front of the spectrometer inlet.



The PE spectra of SSO and OSO (Fig. 1) do not overlap completely in any region, so that the first six bands from SSO can be identified unambiguously.

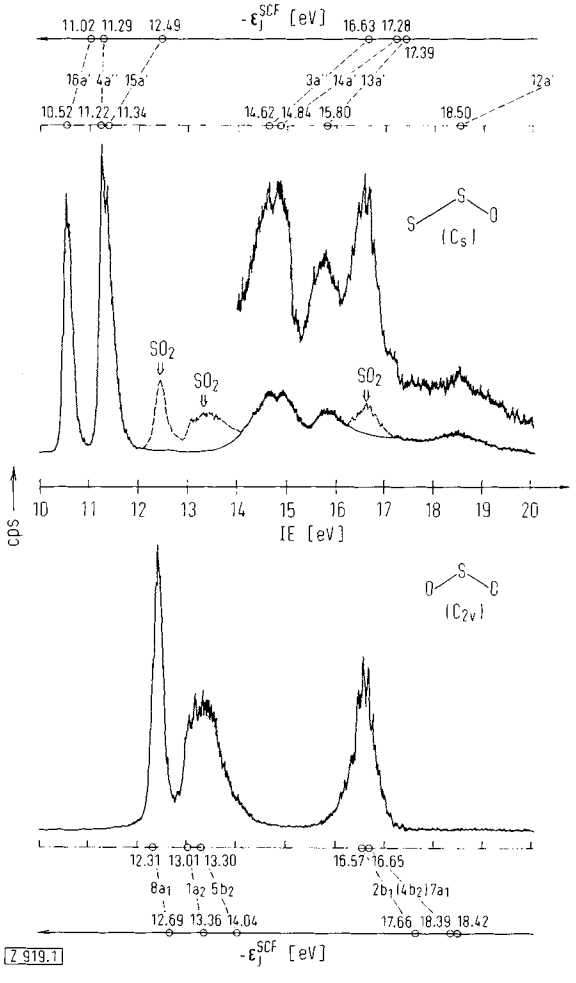


Fig. 1. PE spectra of SSO and OSO (- - - impurity SO_2) with assignment according to *ab initio* orbital energies $-\varepsilon_j^{SCF}$.

For the assignment of the SSO ionization energies IE_n an *ab initio* SCF calculation was carried out with inclusion

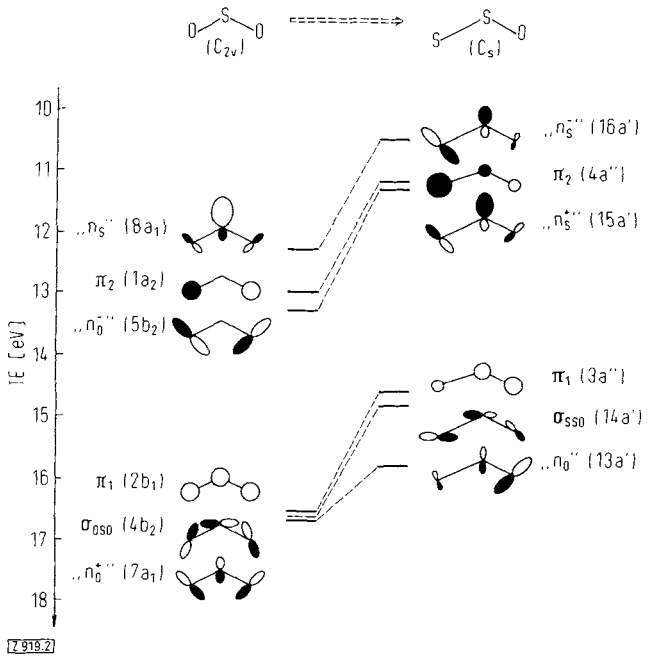


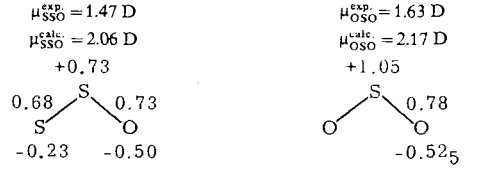
Fig. 2. Orbital correlation OSO→SSO.

of d orbitals (gaussian basis S: 12*s*/9*p*/1*d*; O: 9*s*/5*p*/1*d*), which affords a total energy close to the attainable quality, the Hartree-Fock limit. The calculated orbital energies $-\varepsilon_j^{SCF}$ are listed in Figure 1 together with those for OSO[7]. The assignment, made on the assumption that Koopmans' theorem $-\varepsilon_j^{SCF} = IE_n$[8] is valid, can be partly supported by the vibrational fine structures visible in the spectra[5,6].

The differences in the PE spectra of SSO and OSO are illustrated by the orbital diagram in Figure 2: The replacement O→S raises all the orbitals because of the lower effective nuclear charge of sulfur. At the same time the symmetry C_{2v} is lowered to C_s and thus additional mixing becomes possible for the orbitals which are now of the same symmetry type.

This leads for instance to the result that the oxygen electron pair orbitals $1a_2$ and $5b_2$ non-bonding in OSO obtain in SSO preponderant sulfur contributions (→4*a*" and 15*a*'). It is also easily recognized that the almost energetically degenerate orbitals π_1, σ_{OSO} and n_0^+ in OSO—in the PE spectrum (Figure 1) all of them are assigned to the band at 16.6 eV[5]—on replacement O→S will split due to then different contributions from sulfur; correspondingly the PE spectrum of SSO shows three separate bands (Fig. 1).

In the ground state SSO and OSO have dipole moments μ of comparable size[1,7], the small difference between them being satisfactorily reproduced by the calculations. Nevertheless, the calculated charge distributions and bond (overlap) populations[6,7] differ characteristically:



Obviously, for SSO there results an unsymmetrical charge distribution with unequally charged sulfur atoms. The SO bond population, being reduced relative to OSO, reflects the longer SO bond length in SSO. Comparison of the SO and SS bond populations leads to the conclusion that the S—S double bond is weaker than the S—O double bond.

Like OSO, SSO is thermodynamically stable with respect to elemental sulfur and oxygen[2,6]. Its tendency to polymerize is derived, according to the SCF calculation[6] that can be correlated with the PE spectrum, from the polarizable sulfur-sulfur double bond.

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German version: Angew. Chem. 85, 987 (1973)

[1] Part 25 of Photoelectron Spectra and Molecular Properties.—Part 24: *K.-H. Ostoja-Starzewski, H. tom Dieck,* and *H. Bock,* J. Organometal. Chem., in the press.

[2] *P. W. Schenk* and *R. Steudel,* Angew. Chem. 77, 437 (1965); Angew. Chem. internat. Edit. *4,* 402 (1965); and references cited there.

[3] *P. W. Schenk* and *R. Steudel,* Z. Anorg. Allg. Chem. *342,* 253 (1966).

[4] Sulfur-sulfur bond lengths range from 1.860 Å in F_2SS through 2.05 Å in HSSH to 2.58 Å in S_4N_4 [*R. L. Kuczkowski,* J. Amer. Chem. Soc. *86,* 3617 (1964); 'Interatomic Distances', Spec. Publ. 11 and 18, Chem. Soc. London 1958 and 1965; *B. D. Sharma* and *J. Donohue,* Acta Crystallogr. *16,* 891 (1963)]. According to *I. Lindqvist* [J. Inorg. Nucl. Chem. *6,* 159 (1958)] an SS bond with $d_{SS} \leq 2.58$ Å has no 3*s* component and one with $d_{SS} = 2.08$ Å has 22% 3*s* component. Further shortening is explained by *J. L. Kice* [in *A. Senning:* Sulfur in Inorganic and Organic Chemistry, Vol. 1, Marcel Dekker, New York 1971, pp. 155ff.] by back-bonding to the unoccupied sulfur orbitals.

[5] *D. R. Lloyd* and *P. J. Roberts,* Mol. Phys. *26,* 225 (1973); and references cited there.

[6] For details of the calculations and for further results, also including the isoelectronic NSF, see *P. Rosmus, B. Solouki,* and *H. Bock,* to be published.

[7] *B. Roos* and *P. Siegbahn,* Theor. Chim. Acta *21,* 365 (1971).

[8] *T. Koopmans,* Physica *1,* 104 (1934); cf. *C. R. Brundle* and *M. B. Robin,* Determination Org. Struct. Phys. Methods *3,* 12 (1971).

ABSTRACTS

Reviews

Abstracts of selected progress reports and review articles

The reaction of nitriles with acyl chlorides in the presence of hydrogen chloride is treated by *S. Yanagida* and *S. Komori.* This reaction represents a new route to six-membered heterocycles and novel reactive open-chain compounds. The initial step is seen in attack by the acyl chloride on the N atom of the intermediate imidoyl chlorides or α-chloro enamines formed from nitrile and HCl. The intramolecular reactions lead, *e.g.*, to quinazoline, isoquinoline, 2-pyridone, 1,3-benzothiazine derivatives. The intermolecular reaction of nitriles with acyl chlorides, *e.g.* malonyl chloride, permits synthesis of 1,3-oxazines, 2-pyridones, 3,4-dihydropyrimidines, and reaction with phosgene to synthesis of pyrimidines, 1,3-dichloroisoquinolines, α,β-unsaturated isocyanates and 1,3,5-triazines. Reactions at the N atom of the α-C atom of nitriles are also possible. [The Re-

action of Nitriles with Acyl Chlorides in the Presence of Hydrogen Chloride. Synthesis *1973*, 189—202; 39 references]

[Rd 652 IE—M]

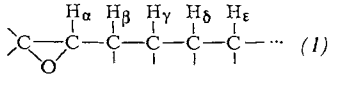
The problem of competitive coordination in complexes is reviewed by *A. D. Garnovskii, O. A. Osipov*, and *S. B. Bulgarevich*. The object of study is the position of the coordinative bond in systems possessing several potential electron donor centers. The authors conclude from numerous examples that the problem is soluble in nonconjugated systems in terms of the concept of hard and soft acids and bases. Complications arise in conjugated systems. [The Principle of Hard and Soft Acids and Bases and the Problem of Competitive Coordination in Complex Compounds. Russ. Chem. Rev. *41*, 341—359 (1972); 441 references]

[Rd 625 IE—Q]

The structures of the rare-earth silicates is reviewed by *J. Felsche*. Owing to their relatively large cations, these silicates contain isolated SiO_4 tetrahedra, Si_2O_7, and Si_3O_{10} groups. The cations show six- to ten-fold oxygen coordination. The types of structures found in this group and their stability ranges, which depend on the cation size, are described. In keeping with the topic, the review is rich in figures and tables of structure data. [The Crystal Chemistry of the Rare-Earth Silicates. Struct. Bonding *13*, 99—197 (1973); 90 references]

[Rd 655 IE—H]

Base-catalyzed rearrangements of epoxides are reviewed by *V. N. Yandovskii* and *B. A. Ershov*. Depending on the structure of the epoxide *(1)* it is possible to abstract an



(1)

α-, β-, or more distant proton with strong bases. The authors describe the subsequent reactions of the resulting carbanions. Since epoxides play an important role in the biogenesis of natural products such reactions could be of interest as models. [Base-catalyzed Rearrangements of Epoxides. Russ. Chem. Rev. *41*, 403—410 (1972); 135 references]

[Rd 656 IE—Q]

Biological and biochemical phenomena of pheromonal action are discussed for the specific example of lepidopteral sex attractants by *P. Karlson* and *D. Schneider*. Many insect pheromones are chemically related to bombykol from *Bombyx mori*. They are long-chain alcohols, aldehydes, and esters, presumably formed from long-chain fatty acids, or terpenoids. The pheromones are transported by diffusion and convection and on reaching the antennae they travel by diffusion to the receptor cell membrane where they interact with an acceptor molecule by way of weak binding forces. The pheromone stimulation releases an electrical potential (electroantennogram) whose characteristic reveals the specificity of the receptors. The question of the evolution of the highly specialized pheromone systems and their further development are discussed, as well as their species specificity. [Sexualhormone der Schmetterlinge als Modelle chemischer Kommunikation. Naturwissenschaften *60*, 113—121 (1973); 133 references]

[Rd 649 IE—M]

Ebullioscopy with salt solutions as "solvents" is described by *B. Magyar*. Solutions of salts in molecular solvents do not show a linear connection between colligative properties and concentration. Therefore such measurements are generally useless for the investigation of the ionic structure of salts, since extrapolation to zero concentration is impossible. This drawback is avoided by "salt ebullioscopy": the vapor pressures above two salt solutions, both in equilibrium with solid salt, one containing some foreign salt, are compared *via* the temperature difference between the solutions that develops in the common solvent vapor atmosphere. One obtains a linear relation of measured temperature difference *vs.* molality of foreign salt; thus, *e.g.*, the number of solute particles per formula weight of foreign salt can be determined. The method is particularly valuable for the investigation of the ionic structure of complex salts, an application which is illustrated with examples. [Salzebullioskopie. III. Theorie und Anwendung zur Bestimmung des Kondensationsgrades polynuklearer Metallkomplexe. Struct. Bonding *14*, 111—140 (1973); 22 references]

[Rd 653 IE—H]

Chalcogeno compounds of transition metals with d^0 electron configuration are reviewed by *E. Diemann* and *A. Müller*. Compounds of this type are so far known with central ions of Groups V, VI, and VII. The authors consider preparative chemistry, formation and decomposition in solutions, thermal decomposition, analytical use, industrial significance, and structural and spectroscopic properties. [Schwefel- und Selenverbindungen von Übergangsmetallen mit d^0-Konfiguration. Coord. Chem. Rev. *10*, 79—122 (1973); 222 references]

[Rd 654 IE—H]

The chemical effects of laser beams are described by *Yu. P. Yampol'skii*. A brief review is given of the various types of lasers and of the properties of laser beams. Lasers can be utilized for the generation and study of short-lived excited states. A number of examples illustrate the high specificity of laser-induced reactions. [Chemical Effects of Laser Radiation. Russ. Chem. Rev. *41*, 529—549 (1972); 140 references]

[Rd 664 IE—Q]

The use of reversed gas chromatography in the study of polymers is described by *V. G. Berezkin* and *A. M. Genkin*. Classical gas chromatography is unsuitable for polymer analysis because the high-molecular compounds are not volatile. This problem can be circumvented by utilizing destructive gas chromatography, which exploits the relationships between the gas chromatogram of the pyrolysis products and the original polymer structure. An alternative method uses reversed gas chromatography, in which the polymer under investigation is employed as carrier for the stationary phase on which volatile standard substances are separated. The behavior of the standard substances provides information about the composition, structure, and other properties of the polymer system. [Use of Reversed Gas Chromatography in the Investigation of Polymeric Compounds. Russ. Chem. Rev. *41*, 542—553 (1972); 67 references]

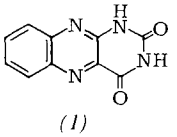
[Rd 665 IE—Q]

Reactions of the radicals $RO^{\cdot}$, $RS^{\cdot}$, and $RO_2^{\cdot}$ with phosphites and phosphanes have been studied by *D. G. Pobedimskii, N. A. Mukmeneva*, and *P. A. Kirpichnikov*. The article first provides a quantitative description of the kinetics of these reactions, and then applies this knowledge to mechanistic investigations on the free-radical oxidation of polymers. Phosphites inhibit these reactions by radical exchange. [Reaction of $RO^{\cdot}$, $RS^{\cdot}$, and $RO_2^{\cdot}$ Radicals with Phosphites and Phosphines. Russ. Chem. Rev. *41*, 555—564 (1972); 49 references] [Rd 666 IE—Q]

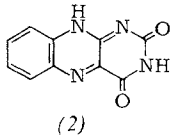
The association of hydrocarbon hydroperoxides is reviewed by *O. P. Yablonskii, V. A. Belyaev*, and *A. N. Vinogradov*. The hydroperoxides can associate with themselves, with alcohols, aromatic compounds, dienes, and olefins by way of inter- and intramolecular hydrogen bonds. The mechanism and thermodynamics of these reactions are described. [Association of Hydrocarbon Hydroperoxides. Russ. Chem. Rev. *41*, 565—573 (1972); 53 references] [Rd 667 IE—Q]

Cleavage of C—N bonds in heterocycles is described by *E. I. Levkoeva* and *L. N. Yakhontov*. Electrophilic reagents such as acids, acid anhydrides, esters, and acyl halides can cleave the C—N bond. von Braun degradation of amines and reactions under inverse Ritter conditions are considered in detail. [Cleavage of Saturated Nitrogen-Containing Heterocycles at the C—N Bond by Electrophilic Reagents. Russ. Chem. Rev. *41*, 603—615 (1972); 137 references] [Rd 669 IE—Q]

The reactivity of alloxazines *(1)* **and isoalloxazines** *(2)* is the topic of a review by *V. M. Berezovskii, L. S. Tul'chinskaya*, and *N. A. Polyakova*. *(1)* and *(2)* represent the



(1)



(2)

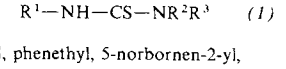
parent compounds of biologically important substances such as riboflavin (vitamin B_2) and flavine adenine dinucleotide (FAD). The review considers, *inter alia*, tautomerisms, oxidations, reductions, and nucleophilic and electrophilic substitutions. [Reactivities of Alloxazines and Isoalloxazines. Russ. Chem. Rev. *41*, 574—591 (1972); 245 references] [Rd 670 IE—Q]

Patents

Abstracts of selected "Deutsche Offenlegungsschriften" (DOS), *i. e.* provisionally published specifications as filed with the German Patent Office

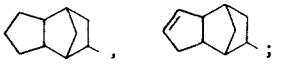
To prepare flame-resistant and hydrolysis-resistant polyurethanes containing chemically bound phosphorus, reaction products of a chloroalkyl phosphorochloridate containing on average 0.5—2.5 chlorine atoms bonded directly to a phosphorus atom in the molecule and a primary or secondary amine, possibly containing other functional groups (*e.g.* aminoalkanol or iminodialkanol, ethylenediamine, piperazine) are used as flameproofing phosphorus compounds that can be incorporated. The reaction is carried out at 0—100 °C in the presence of excess propylene oxide as a hydrogen chloride acceptor, practically one molecule of amine being used per chlorine atom in the chloroalkyl phosphorochloridate. The chloroalkyl phosphorochloridate is prepared by reaction of phosphorus oxide chloride with ethylene or propylene oxide (molar ratio 1 : 0.5—2.5) at 0—100 °C in the presence of a catalyst such as pyridine or phosphorus trichloride. The resulting phosphorus compounds are generally amber-colored, hydrolysis-resistant liquids that react with organic polyisocyanates and possibly phosphorus-free polyols (*e.g.* polypropylene oxide) to form polyurethanes having good mechanical properties and excellent flame resistance. [DOS 1745191; Naphthachimie, Paris] [PR 63 IE—Ö]

Fruits can be made to fall and can thus be harvested more economically if the fruit-bearing trees or bushes are treated with an agent containing a thiourea derivative *(1)* shortly before the fruits ripen. Some mechanical assis-



(1)

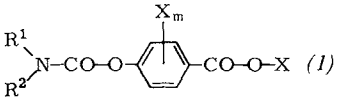
R^1 = (substituted) phenyl, allyl, benzyl, phenethyl, 5-norbornen-2-yl,



R^2 = H, allyl, alkyl, alkoxy; R^3 = H, (substituted) phenyl, alkyl, alkenyl, chloroalkenyl, dialkylamino, furyl; $R^2 + R^3$ = alkylene

tance may be necessary. [DOS 2157288; Ciba-Geigy AG, Basel] [PR 97 IE—N]

Substituted *p*-carbamoyloxybenzoic esters *(1)* are biocides for paints. They are compatible with the usual resin binders, are not discolored by sulfides, do not influence the physicochemical properties of the paints, and protect them against



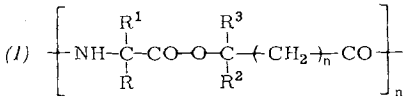
(1)

R^1 = alkyl (C_1—C_{13}), alkenyl (C_2—C_8), $-(CH_2)_n-NR^2-CO-O-p-C_6H_3X'_m-CO-O-X$; R^2 = H, alkyl (C_1—C_5); X = alkyl (C_1—C_5), $-(CH_2)_n-OH$, $-(CH_2)_n-O-CO-NR^1R^2$; X' = alkyl (C_1—C_5), alkoxy (C_1—C_5); m = 0, 1, 2; n = 2—6

attack by fungi and other microorganisms. [DOS 2207729; Tenneco Chemicals, Inc., New York] [PR 116 IE—N]

Acrylonitrile copolymer films, fibers, and filaments having stable luster consist of 95 to 70 parts by weight of a copolymer of acrylonitrile with 35 to 60 wt.% of vinylidene chloride and 5 to 30 parts by weight of a homopolymer of *N*-vinylpyrrolidone. A disadvantage that has been found with the usual copolymers of acrylonitrile with vinylidene chloride and/or vinyl chloride is that the luster decreases when the products come into contact with water or steam at high temperatures. [DOS 2128004; Bayer AG, Leverkusen] [PR 120 IE—A]

A novel surgical suture material, which is hydrolyzed within four to six weeks at the pH of human body fluids and largely retains its tensile strength during this time, is obtained by spinning the copolymers *(1)* of amino and



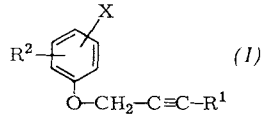
(1)

R = alkyl (C_1 to C_5), aryl, alkylaryl, or aralkyl; R^1, R^2, and R^3 = hydrogen or lower alkyl residues, at least one of these residues necessarily being hydrogen; n = whole number from 0 to 2

hydroxy carboxylic acids. The favorable hydrolysis properties are due to the fact that the copolymers contain both ester linkages and amide linkages in the main chain. They are prepared by reaction preferably of 2,5-oxazolidinediones with the lactones or anhydrosulfites of the hydroxy acids in the absence of moisture and air. [DOS 2162157; Suture Inc., Coventry, Conn. (USA)]

[PR 122 IE—S]

Aryl alkynyl ethers such as *(1)* exhibit insecticidal, particularly lepidoptericidal, and herbicidal activity. They can be used as selective insecticides. Preparation is from a



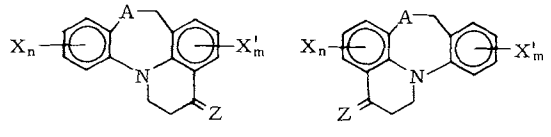
(1)

R^1 = H, alkyl; R^2 = alkynyloxy, alkynylthio, alkenyloxy, haloalkenyloxy, alkoxy, alkynyloxycarbonyl; X = H, CN, CO—NH_2, CHO, halo, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkynyloxy, alkoxycarbonyl, alkynyloxycarbonyl

phenol and a propargyl halide in the presence of an acid acceptor in an inert solvent. [DOS 2156920; Stauffer Chemical Co., New York]

[PR 96 IE—N]

Partly hydrogenated quinolinobenzazepines *(1)*—*(4)* can be used to combat infections due to organisms such as *Trichomonas vaginalis*, *Staphylococcus aureus*, *Salmonella schottmuelleri*, and *Candida albicans*, and also as surface antiseptics. *(1)* and *(3)* can be synthesized by cyclization



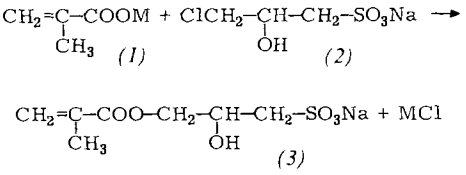
(1), Z = O
(2), Z = NOH
(3), Z = O
(4), Z = NOH

X,X' = R, —S—R, —O—R, halogen, CF_3, CN, SO_2—NR_2; R = lower alkyl; A = O, S, SO, SO_2; n,m = 0, 1, 2

of the *N*-(dibenzazepine)propionic acid or its acyl chloride; depending on the number, nature, and position of X and X', one obtains *(1)* and/or *(3)*. *(2)* and *(4)* are obtained from *(1)* and *(3)* respectively with hydroxylamine. [DOS 2153589; E. R. Squibb & Sons Inc., New York]

[PR 101 IE—N]

To prepare esters *(3)* **of 2,3-dihydroxy-1-propanesulfonic acid with alkenecarboxylic acids,** the salts *(1)* (M = alkali metal or alkaline earth metal) and *(2)* (possibly the acid) are allowed to react in the presence of polar solvents, *e.g.*:



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

Despite the OH group, one obtains pure polymerizable esters that allow the preparation of pure polymers. The new esters *(3)* are used for the preparation of fibers, antistatics, cleaning, wetting, and dispersing agents, ion exchange resins, and plastics. [DOS 2104868; Badische Anilin- & Soda-Fabrik AG, Ludwigshafen]

[PR 103 IE—B]

Fire-resistant, loaded melt compositions based on atactic polyolefins, which offer technical advantages for coatings and adhesive applications of all kinds because of their freedom from solvent and their fast setting properties, contain as the flame-resistant agents 0.1—10 parts by weight of Sb_2O_3 and 1—10 parts by weight of chloroparaffin with 30—70 parts by weight of chlorine and 5—85 parts by weight of fillers that are less reactive than Sb_2O_3 toward halogen and halogen compounds; in particular, they contain barite as filler. [DOS 2105187; Veba-Chemie AG, Gelsenkirchen-Buer]

[PR 105 IE—Z]

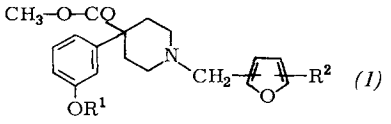
To prepare flexible phenolic resins that cure at relatively low temperatures (160—180 °C) and/or in a short time, that are resistant to chemicals, and whose plastic behavior is also adequate for surface protection, 1 mole of bis(hydroxymethyl)alkylphenol (C_{1-20} in the alkyl residue) is condensed with 1.4 to 1.6 moles of the hydroxymethyl compounds of polyfunctional phenols in which at least half of the reactive H atoms are replaced by hydroxymethyl groups. The hydroxymethyl compounds both of the alkylphenols and of the polyfunctional phenols may be at least partly etherified with monofunctional or polyfunctional aliphatic alcohols containing 1—20 C atoms. [DOS 1770816; Chemische Werke Albert, Wiesbaden-Biebrich]

[PR 108 IE—Z]

Use of high-frequency microwave energy in graft copolymerization of ethylenically unsaturated compounds on a water-insoluble "thioated substrate" in the presence of a free-radical initiator considerably shortens the time required for the grafting of appreciable quantities of monomer under mild conditions. This process is used in particular for the printing of two-dimensional products. The printing pastes contain at least one ethylenically unsaturated monomer (*e.g.* acrylamide ± *N*-hydroxymethylacrylamide or ethyl acrylate ± acrylic acid ± *N*,*N*-dimethylaminoethyl methacrylate), peroxide initiators (H_2O_2), and a pigment or a dye. They are printed on a two-dimensional product made from the thioated substrate, in particular on a dithiocarbonated (with CS_2) derivative of cotton, rayon, cellophane, jute, wood, cellulose acetate, wool, silk, or nylon; finally, the areas on which the paste has been deposited are exposed to microwaves. [DOS 2204442; Scott Paper Co., Industrial Highway at Tinicum Island Road, Delaware County, Pa.]

[PR 109 IE—Z]

1-Furylmethyl-4-methoxycarbonyl-4-phenylpiperidines *(1)* and their acid-addition salts have a non-morphine-like, strong analgesic activity and are therefore non-habit-forming analgesics. They can be obtained by conventional



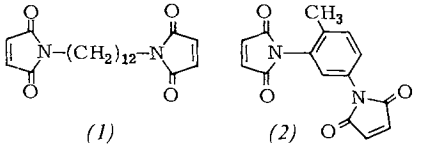
(1)

$R^1 = H, CH_3$; $R^2 = H, CH_3, C_2H_5$; X = halogen, $-O-SO_2$-alkyl, $-O-SO_2$-aryl

methods, *e.g.* by reaction of the piperidine grouping with furylmethyl derivatives or with formaldehyde and furan derivatives. [DOS 2109155; C. H. Boehringer Sohn, Ingelheim]

[PR 112 IE—N]

Poly-1,12-bis(maleimido)dodecane and poly-2,4-bis(maleimido)toluene are obtained by thermal polyaddition of the monomers *(1)* and *(2)* above their melting points. Poly-1,12-bis(maleimido)dodecane is formed as an intensely



(1) *(2)*

brown-yellow, dense substance, and poly-2,4-bis(maleimido)toluene as an intensely yellow, dense substance. Both polymers are crosslinked, are insoluble in organic media, and do not melt without decomposing. They have good mechanical properties even above 200 °C, and can be used for the production of heat-resistant molded articles such as fiber-reinforced coil formers. [DOS 2165979 + DOS 2165982; Technochemie GmbH, Heidelberg]

[PR 123 IE—S]

Plastics having the ability to retain electrostatic charges are obtained if compounds containing polar groups are incorporated into the polymers by known methods. Silicone oligomers and polymers, aromatic oligomers and polymers, and polymers and copolymers of acrylic and methacrylic acids and their esters may be used as the polymers, and alcohols, metal hydroxides, chlorine-carbon compounds, carbonyl compounds, and organic acids and their metal salts as the compound containing polar groups. If a charge is applied to the surface of the polymer, its electric conductivity decreases in the xerographic sense. [DOS 2217645, Xerox Corp., Rochester]

[PR 131 IE—E]

Polymeric hydrogels with high water contents, *e.g.* 55 to 85%, are obtained by copolymerization of a hydroxyalkyl acrylate or methacrylate and a vinyl comonomer that has a greater affinity for water than a homopolymer of the hydroxyalkyl acrylate or methacrylate in the presence of a crosslinking monomer, *e.g.* an ethylene dimethacrylate or diacrylate. Contact lenses can be made from the copolymers. Their good tolerance by the human eye is assumed to be at least partly due to the similarity of the water contents of the lenses and of the cornea. [DOS 2205391; John T. de Carle, London]

[PR 117 IE—E]

BOOK REVIEWS

Transition Metal Hydrides. Vol. I. The Hydrogen Series. By *E. L. Muetterties, B. A. Frenz, J. A. Ibers, J. P. Jesson, R. A. Schunn,* and *C. A. Tolman.* Marcel Dekker Inc., New York 1971. 1st ed., xv, 342 pp., numerous figures, bound $ 14.50.

The first volume of the new series "The Hydrogen Series" deals with the topical subject of transition metal hydrides. Since good reviews on binary transition metal hydrides have already been published, only a short chapter (22 pages) is devoted to this sector. Also for the sake of completeness, the volume is introduced by a brief outline of the physical properties of hydrogen and its isotopes. Many literature references are given for both chapters.

The actual theme of the book, the hydrido complexes of the transition metals, is introduced in the third chapter. This begins with the problem of the localization of hydrogen in structural analyses, which is followed by a well illustrated survey of all the crystal structure investigations that have now been published. The subsequent part of the book, which is the largest section, deals with the stereochemistry of the hydrido complexes in solution. A critical survey of the measuring methods that can be used for the determination of structures (with special reference to NMR and IR) is followed by a description of the structures found for the complexes. NMR data in particular are presented and discussed here. The chapter ends with a discussion on non-rigid systems. The fifth chapter deals with the preparation of the hydrido complexes, arranged according to synthesis methods, and with their reactions. Since the index of the book is very inadequate with regard to this very chapter, the search for a given compound can be very time-consuming. Improvement of the index or the inclusion of a table arranged according to substances at the end of the chapter would be desirable. The last chapter deals with homogeneous catalysis, particularly with the change in the properties of the ligands as a result of complexing, and with the reactions of the M—H bond. Special emphasis is placed here on reaction mechanisms.

The book covers the literature up to and including 1970. Chapters 3, 4, and 5 can make some claim to being substan-

tially complete. On the whole this volume is a good start to the new series. It can be strongly recommended to all those who wish to gain a detailed understanding of the hydrido complexes of the transition metals.

Mathias Höfler [NB 155 IE]

Chemical Analysis of Additives in Plastics. By *T. R. Crompton*. Pergamon Press, Oxford—New York 1971. 1st ed., xi, 162 pp., numerous figures, bound £ 7.—.

Few plastics are used at present without additives such as plasticizers or stabilizers. The identification and determination of such substances is frequently necessary for a wide variety of reasons, but is very difficult and expensive in some cases. The very extensive literature in this field is widely scattered and often applicable only to very special cases, so that there is a clear need for a good survey that would be of use to the practical worker.

The present book deals with the analysis of additives, not according to their chemical structure or fields of use, but mainly from the standpoint of methods. The qualitative analysis of known additives (phenolic and amine antioxidants, plasticizers, UV absorbers, peroxides, and various monomers) by spectroscopic methods and by thin layer and column chromatography is discussed in the first two chapters. The chromatographic methods, partly in combination with spectroscopy, for the identification and quantitative determination of unknown additives are then considered; the final chapter contains examples of the applications of gas chromatography, and the determination of monomers and volatile impurities is also discussed.

In comparison with the existing literature, the total of 330 references is rather small, but they cover the principal topics, though sometimes in a very arbitrary selection. The experimental data in the book are too concise in most cases, so that they cannot be followed directly in practice. One major disadvantage is that practical procedures and descriptive passages follow one another with little rhyme or reason, so that it is often very difficult to obtain a general picture. Little help is offered in this respect by the very brief list of contents and the index, which includes only about 170 keywords.

Apart from these limitations, the book will undoubtedly be a useful aid to the experienced plastics analyst, and should have a place in every reference library in this field. In a second edition, we would like to see a better arrangement and the inclusion of a greater number of more critically selected practical procedures.

Dietrich Braun [NB 157 IE]

Oxidation-Reduction Potentials of Inorganic Substances in Aqueous Solution. IUPAC—Selected Constants. By *G. Charlot, A. Collumeau*, and *M. J. C. Marchon*. Butterworths, London 1971. 1st ed., 73 pp., bound £ 3.50.

With the support of employees from the Laboratoire de Chimie Analytique, Paris, and from the Centre National de la Recherche Scientifique, *G. Charlot et al.* in the Electrochemical Commission of the Analytical Chemistry Division of the IUPAC have compiled a collection of data that should be useful to any inorganic chemist. The data refer mainly to complexes with oxide, hydroxide, halide, azide, cyanide, and thiocyanate as ligands. Complex redox pairs with organic ligands are unfortunately not tabulated. It is left to the reader to calculate these for himself from the data given and from constants tabulated elsewhere for complex equilibria.

Standard potentials (based on the activity $a=1$) and formal potentials (based on the concentration $c=1$) are listed separately; this takes into account the requirements of thermodynamically correct terminology. Though the majority of the potentials given are for 25 °C, the corresponding temperature is given in every case. An important advantage for comparison purposes is that the method used for the determination of the literature value is also indicated.

This tabulation covers the literature from 1900 up to December 31, 1967. The arrangement in alphabetic order of the elements is based on practical requirements, though it makes comparisons within individual chemical groups more difficult. About a dozen half-cell reactions contain errors of stoichiometry, and should be corrected with respect to the balance of particles and charges. Moreover, the symbols Es (instead of En) for einsteinium and Md (instead of Mv) for mendelevium should have been used.

To sum up, it may be said that this tabulation of about 100 redox potentials in a small volume should be a useful addition to the existing collections of data.

Norbert Kirsch [NB 159 IE]

The Identification of Organic Compounds. By *S. Veibel*, G. E. C. Gad Publisher, Copenhagen 1971. 7th ed., xvi, 471 pp., numerous figures, bound Dk 115.—.

Six years after its last edition, this well-established book is now available in its 5th English edition. The book contains the chemical methods for the detection and determination of organic compounds. The first section deals with the testing of purity, and includes chromatographic methods as one of its new features. The second section contains the methods for the detection and determination of the elements, while general methods for the examination of organic substances are given in the third section. The last and by far the largest chapter contains the methods for the detection and determination of functional groups.

In comparison with the last edition, methods that have proved less useful have been eliminated and new methods have been introduced. The latter include in particular the methods of titration in non-aqueous media. The book ends with a table of a wide range of reagents in the required concentrations and a large author and subject index.

It is undoubtedly difficult to bring a book that first appeared in 1927 up to date by constant additions and revisions. Nevertheless, this book is certainly useful and can be recommended, as long as one is interested only in chemical methods. However, the claim that can be inferred from the title cannot be upheld when one considers that spectroscopic methods, which are dominant today, are practically ignored.

Hermann Stetter [NB 162 IE]

Organosilicon Derivatives of Phosphorus and Sulfur. Monographs in Inorganic Chemistry. By *S. N. Borisov, M. G. Voronkov*, and *E. Ya. Lukevits*. Plenum Press, New York—London 1971. 1st ed., xiv, 343 pp., numerous tables and formulas, bound $ 28.—.

An element whose first organo derivatives were prepared to disprove *Mendeleev*'s system, whose second encounter with organic chemistry was motivated by the idea of using organosilicon compounds for the study of optical activity (which did not work either, at least not in this way), and which only at the third attempt found a

significant position in organoelement chemistry thanks to the technical breakthrough of organosilicon chemistry, may surprise the reader not familiar with the growth rate of its literature by now having an entire book published on only two special groups of compounds, *i.e.* organo derivatives of silicon and phosphorus and of silicon and sulfur.

This is a very concisely arranged and instructively written book by authors who have themselves made substantial contributions in this field and in whose country this branch of chemistry receives particular attention. The first 140 pages are devoted to the chapter on organosilicon derivatives of phosphorus, and a further 176 pages to the chapter on organosilicon derivatives of sulfur, both chapters being divided into sections according to characteristic bonds, *e.g.* Si—O—P, —O—S—P, —N—P, —C—P, —C—O—P, and Si—S—H, —S—C, —S—Si, —O—S, —N—S, —NCS, —C—S, —C—S—C. These sections begin with preparative methods; a few examples are used for the discussion of the behavior of the classes of substances in question, and the physical data for the various compounds are given, mostly in tabulated form.

As a result, the picture of the organoelement compounds from this part of the periodic system has been rounded off, analogies and relationships have come out, and differences have become less pronounced. The book will be rewarding both to the fundamental scientist and to those active in this field; it has much to offer to the advanced student also.

Walter Simmler [NB 161 IE]

Reaction Mechanisms in Sulfuric Acid and other Strong Acid Solutions. By *M. Liler*. Academic Press, London—New York 1971. 1st ed., xiii, 350 pp., numerous figures and tables, bound £ 6.—.

The investigation of organic compounds in very strong acids has been carried on intensively during the past few years and has led to a whole series of unique findings. A comprehensive monograph on the reaction behavior of mainly organic substances in sulfuric acid, which is probably the most versatile and the most interesting of the strong acids from the historical point of view, is therefore very welcome.

After a brief historical introduction, the first section deals with the physical (density, viscosity, conductivity, *etc.*), thermodynamic (phase transitions, heat capacity, *etc.*), and spectroscopic (Raman, IR, UV, NMR) properties of sulfuric acid/water mixtures. The section ends with a brief discussion of dideutero and ^{35}S-sulfuric acid (25 pp.). The second section is devoted to the acidity functions. The acidity functions for simple protonations, protonations of olefins, and complex ionizations are considered. The individual acidity functions (H_0, H_0', H_A, H_I, H_+, H_R, *etc.*) and their physical significance are then briefly discussed (33 pp.). The third section deals with the protonation of very weak bases, the experimental methods for the determination of basicity in sulfuric acid being discussed in the first part and individual classes of compounds with nitrogen, phosphorus, oxygen, *etc.* as the basic center, as well as basic hydrocarbons, in the second part (86 pp.). Complex ionizations of organic and inorganic substances (determination and discussion of their *i* factors) are the subject of the fourth section. The fifth and final section takes up about half of the book (139 pp.) and has the same title as the book itself. After a general discussion of the main reaction types in strongly acidic solutions, individual classes such as hydrolysis, hydration, isomerizations and rearrangements, decarbonylation and decarboxylation, electrophilic aromatic substitution, and special cases of carbonium ion reactions are discussed.

On the whole the book gives a good and comprehensive survey of reactions in sulfuric acid, the emphasis generally being placed on quantitative aspects. Preparative problems are left somewhat in the background. In the discussion of cyclizations in strong sulfuric acid, for example, a comparison with hydrogen fluoride or polyphosphoric acid would have been valuable to the organic chemist. In the discussion of the reactions of azides, one finds no reference to the extensive work of *Bamberger* on the decomposition of aryl azides in strong acids.

Hans-Jürgen Hansen [NB 165 IE]

The Radiation Chemistry of Water. By *I. G. Draganić* and *Z. D. Draganić*. Academic Press, London—New York 1971. 1st ed., xi, 242 pp., numerous figures and tables, bound $ 14.—.

Great advances, resulting in numerous publications, have been achieved in the field of the radiation chemistry of water during the past ten years, mainly through the discovery of the hydrated electron and the development of the pulse radiolysis technique.

Much of the recent knowledge is surveyed in the present monograph, which is strictly confined to the radiation chemistry of liquid water. The authors link up with an account by *A. O. Allen*, which has been one of the standard works on radiation chemistry for ten years.

The book is divided into eight chapters. It begins with a survey of the last 70 years in the radiation chemistry of water. The physical processes involved in the absorption of radiation in water are discussed in detail. Chapters 3 and 4 are devoted to the properties and chemical reactions of the primary radicals produced by radiation, *i.e.* the hydrated electrons, hydrogen atoms, and hydroxyl radicals. These two central chapters are unfortunately very incomplete, and clarity is lost through the repetition of historical considerations.

The radiation-chemical yield (G value) of primary radicals and molecular products (H_2 and H_2O_2) as a function of pH, pressure, temperature, LET, and dose rate has a chapter to itself. This is followed by a discussion of a number of new diffusion-kinetic models with a comparison of data obtained theoretically and experimentally. The book ends with a survey of experimental methods (radiation sources, pulse radiolysis technique, sample preparation, *etc.*) and dosimetry in water and with aqueous solutions.

The long compilation of original literature, which is complete up to 1967 but covered only in part up to 1969, must be specially mentioned, as well as the chapters on the radiation-chemical yield and on the diffusion-kinetic models. Another commendable feature is the summary that precedes each chapter, from which the main ideas can be repeatedly picked out, and which pleasantly break up the description, which is otherwise rigorous and often goes into great detail. The book will undoubtedly be useful to the specialist and to the interested scientist.

Klaus Eiben [NB 168 IE]

Recent Books

The following books have been received by the editor. Detailed reviews will not be published in all cases because of the limited space available under this heading in the journal.

College Chemistry. By *G. B. King, W. E. Caldwell,* and *M. B. Williams.* 6th Edit. Van Nostrand Reinhold Company, New York—Cincinnati—Toronto—London—Melbourne 1972. ix, 696 pp., bound £ 5.65.

Analytical Chemistry of Fluorine. By *N. S. Nikolaev, S. N. Suvorova, E. I. Gurovich, I. Peka,* and *E. K. Korchemnaya.* From the series "Analytical Chemistry of the Elements". Halsted Press, a Division of John Wiley & Sons, New York 1973. xiv, 222 pp., bound £ 9.35.

Contents: Physicochemical and Analytical Description of Fluorine and Fluorine Compounds; Chemical and Physical Methods for the Determination of Fluorine; Separation of Fluorine; Determination of Fluorine in Natural and Industrial Products; Determination of Fluorine in Actinide Compounds; Determination of Fluorine in Water, Air and Biological Objects; Determination of Elementary Fluorine in Gases; Determination of Fluorine, Hydrogen Fluoride, and Impurities in Hydrofluoric Acid and in Liquid Hydrogen Fluoride.

Modern Inorganic Chemistry. By *J. H. Lagowski.* Marcel Dekker, New York 1973. xiii, 806 pp., bound $ 13.75.

Contents: Atoms and Their Characteristics; Ionic Compounds; Covalent Compounds; Theories of Bonding; Hydrogen; Solvent Properties of Covalent Hydrides; Alkali Metals; Alkaline-Earth Metals; Group III Representative Elements; Group IV Elements; Group V Elements; Group VI Elements; The Halogens; The Rare Gases; The Transition Elements; Transition-Metal Complexes: Theoretical Aspects; Organic Derivatives of the Transition Metals.

Grundriss der Biochemie. Für Studierende der Medizin, Zahnmedizin und Naturwissenschaften. By *E. Buddecke.* 3rd Edit. Walter de Gruyter, Berlin—New York 1973. xxxii, 515 pp., stitched DM 29.50.

Ultrarotspektroskopische Untersuchungen an Polymeren. (Infrared Spectroscopic Investigations on Polymers). By *J. Dechant.* Akademie-Verlag, Berlin 1972. xi, 516 pp., bound DM 93.—.

Contents: General Principles of Infrared Spectroscopy; Theory of Infrared Spectroscopy; Experimental Methods of Infrared Spectroscopic Investigations on Polymers; Special Problems of Infrared Spectroscopic Investigations of Polymers: Results of Infrared Spectroscopic Investigations on Special Polymers.

Water and Water Pollution Handbook, Vol. 4. Edited by *L. L. Ciaccio.* Marcel Dekker, New York 1973. xi, 1945 pp., bound $ 29.50.

Contents: Determination of Minor Metallic Elements in the Water Environment; Determination of Radioactive Nuclides in Water; Monitoring of Water Systems; Automated and Instrumental Methods in Water Analysis; Gas Chromatographic Analysis of Water and Waste Waters; Mass Spectrometry in Water Analysis; Infrared Spectroscopy in Water Analysis; Luminescence Techniques in Water Analysis; Electrochemical Techniques in Water Analysis.

Grundlagen der Mathematik. Eine Einführung in die mathematischen Methoden. (Principles of Mathematics. An Introduction to Mathematical Methods.) By *F. H. Young.* Verlag Chemie, Weinheim—John Wiley & Sons, New York 1973. xii, 405 pp., bound DM 44.—.

Contents: Historical Development; Numbers and Number Systems; Set Theory and Logic; Divisibility; Analytical Geometry; Functions; Differential and Integral Calculus; Vectors and Matrices; Computers.

Lebensmittel—Fortschritte in der Verfahrenstechnik der Lebensmittelverarbeitung (Foods—Advances in the Technology of Food Processing). Dechema-Monograph No. 1327—1350 (Vol. 70). Edited by Deutsche Gesellschaft für Chemisches Apparatewesen. Verlag Chemie, Weinheim 1972. 429 pp., bound DM 110.—. 24 lectures, delivered to the 4. European Symposium "Lebensmittel—Fortschritte in der Verfahrenstechnik der Lebensmittelverarbeitung mit besonderer Berücksichtigung der Proteine, Enzyme und Aromen", October 25—28, 1971, in Frankfurt.

Carbenes, Vo. 1. Edited by *M. Jones, Jr,* and *R. A. Moss.* John Wiley & Sons, New York, London, Sydney, Toronto 1973. 356 pp., bound £ 12.50.

Contents: Carbenes from Diazo Compounds; The Application of Relative Reactivity Studies to the Carbene Olefin Addition Reaction; Generation of Carbenes by Photochemical Cycloelimination Reactions.

Mass Spectrometry, Vol. 2. By *D. H. Williams.* The Chemical Society, London 1973. xi, 356 pp., bound £ 8.00.—A volume in the series "Specialist Periodical Reports".

Organic Phosphorus Compounds, Vol. 1. Edited by *G. M. Kosolapoff* und *L. Maier.* Wiley-Interscience, New York, London, Sydney, Toronto 1972. xiii, 545 pp., bound £ 13.25.

Contents: Primary, Secondary, and Tertiary Phosphines; Organophosphorous-Metal Compounds; Biphosphines, Triphosphines; Tetraphosphines, Cyclopolyphosphines, and Corresponding Oxides, Sulfides, and Selenides; Phosphine Complexes with Metals.

Magnetochemie. Grundlagen und Anwendungen. (Magnetochemistry. Principles and Applications). By *A. Weiss* and *H. Witte.* Verlag Chemie, Weinheim 1973. ix, 281 pp., bound DM 59.—.

Contents: Physical Principles of Magnetochemistry; Measuring Methods; Diamagnetism; Paramagnetism; Cooperative Phenomena; Examples of Application of Magnetochemistry to Chemical Problems.

Current Problems in Electrophotography. Edited by *W. F. Berg* and *K. Hauffe.* Walter de Gruyter, Berlin—New York 1972. xv, 387 pp., stitched DM 140.—.—Lectures delivered to the 3rd European Colloquium, Zürich, August 1971.

Chemical Thermodynamics, Vol. 1. By *M. L. McGlashan.* The Chemical Society, London 1973. xii, 362 pp., bound £ 8.00.—A volume in the series "Specialist Periodical Reports".

Developments in Inorganic Nitrogen Chemistry, Vol. 2. Edited by *C. B. Colburn*. Elsevier Scientific Publishing Company, Amsterdam—London—New York 1973. x, 228 pp., bound Dfl. 100.00/$ 31.25.

Contents: Reactions of Nitrogen(II) Oxide; The Chemistry of Dinitrogen Pentoxide; Nitrogen Compounds of Chlorine, Bromide and Iodine.

The Isoquinoline Alkaloids. Chemistry and Pharmacology. By *M. Shamma*. Volume 25 of the series "Organic Chemistry". Academic Press, New York—London—Verlag Chemie, Weinheim 1972. xviii, 594 pp., bound DM 122.—.

Gmelins Handbuch der anorganischen Chemie. 8th Edit., part B 4 Niob, System No. 49. Verlag Chemie, Weinheim 1973. xxiv, 473 pp., bound DM 641.—.

Contents: Oxoniobate der Alkalimetalle; Niobverbindungen mit weiteren Kationen und Anionen; Kohlenstoffverbindungen des Niob.

Industrielle Destillation. By *R. Billet*. Verlag Chemie, Weinheim 1973. xi, 502 pp., bound DM 108.—.

Contents: Die Verfahren der thermischen Flüssigkeitszerlegung; Thermodynamische Grundlagen der Gemische; Kontinuierlich arbeitender Rektifizierapparat; Diskontinuierlich arbeitender Rektifizierapparat; Semi-kontinuierlich arbeitender Rektifizierapparat; Verfahrenstechnische Bewertung, Kostenoptimierung und Auswahl von Kolonneneinbauten; Optimierung der Trennungen; Unterlagen zur Dimensionierung von Trennkolonnen; Partielle Destillation; Partielle Kondensation; Destillation in Laboratoriums- und Technikumskolonnen; Molekulardestillation; Zubehör von Trennanlagen; Einsatz von Computern.

Laboratory Experiments in College Chemistry. By *G. B. King, W. E. Caldwell*, and *M. B. Williams*. 3rd Edit. Van Nostrand Reinhold Company, New York—Cincinnati—Toronto—London—Melbourne 1972. vi, 280 pp., stitched £ 2.60.

Spectroscopy and Kinetics. Edited by *J. S. Mattson, H. B. Mark, Jr.*, and *H. C. MacDonald, Jr.* Vol. 3 of the series "Computers in Chemistry and Instrumentation". Marcel Dekker, New York 1973. xi, 330 pp., bound $ 19.75.

Organic Functional Group Preparations, Vol. 3. By *S. R. Sandler* and *W. Karo*. Vol. 12-III of the series of monographs "Organic Chemistry" Academic Press, New York—London 1972. xi, 496 pp., bound $ 24.50.

Contents: Acetals and Ketals; Anhydrides; Monoalkyl Sulfates; Sulfenic Acids and Sulfenic Acid Derivatives; Isonitriles; Amidines; Imidines; Imidates; Nitrones; Hydroxylamines and Substituted Hydroxylamines; Oximes; Hydroxamic Acids; Thiohydroxamic Acids.

Zerkleinern. Dechema Monograph No. 1292—1326 (Vol. 69). Edited by Deutsche Gesellschaft für Chemisches Apparatewesen. Verlag Chemie, Weinheim 1972. Two parts having a total of 948 pp., bound DM 192.50.—35 Lectures and discussions held at the 3rd European Symposium on "Size Reduction" October 5—8, 1971 at Cannes.

Electronic Transitions and the High Pressure Chemistry and Physics of Solids. By *H. G. Drickamer* and *C. W. Frank*. From the series "Studies in Chemical Physics". Edited by *A. D. Buckingham*. Chapman and Hall, London 1973. x, 220 pp., bound £ 5.00.

Contents: Introduction; Theories of Electronic Energy Levels in Molecules and Solids; Thermal Versus Optical Transitions; Phenomenological Description of Continuous Electronic Transitions; Methods for Studying Electronic Structure at Very High Pressure; Shifts of Energy Levels with Pressure; Electronic Transitions in Metals and Insulator-Metal Transitions; Spin Changes in Iron Complexes; The Reduction of Ferric Iron; Changes of Oxidation State and Spin State; Reactions in Aromatic Molecules and Complexes.

Die Struktur der Proteine. By *H. Fasold*. Vol. 12 of the series "Chemische Taschenbücher". Edited by *W. Foerst* and *H. Grünewald*. Verlag Chemie, Weinheim 1972. x, 298 pp., stitched DM 32.—.

Contents: Aminosäuren und Peptide; Verfahren zur Reinigung und Charakterisierung der Proteine; Aufklärung der Primärstruktur; Raumstruktur der Peptidketten (Sekundär- und Tertiärstruktur); Quartärstruktur von Proteinen; Evolution eines Proteinmoleküls und Determination seiner Tertiär- und Quartärstruktur; Denaturierung von Proteinen; Enzyme; Beispiele einiger Proteinfamilien.

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The "Nickel Effect"

By Karl Fischer, Klaus Jonas, Peter Misbach, Reinhold Stabba, and Günther Wilke[*]

In Memory of Karl Ziegler

Whereas the reaction of ethylene and triethylaluminum under pressure at 100 °C yields trialkylaluminum compounds having long alkyl chains, the presence of small amounts of nickel salts induces the formation of butene. The discovery of this "nickel effect" represents the starting point for the development of the Ziegler catalysts. Comparatively little was formerly known about the nature and the mode of action of the catalytically active nickel species. A basis for the elucidation of the effect was provided by studies on the reduction of nickel compounds by organoaluminum compounds, on the occurrence and existence of nickel hydrides, and on interactions between nickel(0) and Lewis acids as well as organic compounds of main group metals. The most significant result of these studies is the recognition that multicenter bonding systems involving trialkylaluminum compounds and nickel atoms are involved. These react further with complex bonded ethylene in what is probably a concerted manner.

1. Introduction

The appearance of this review practically coincides with the twentieth anniversary of the discovery of the "Nickel Effect" by *Ziegler* and *Holzkamp*[1]. This discovery, the systematic investigation of which led to the Ziegler catalysts[1b, 2], started an avalanche which caused a revolution in certain areas of chemistry, and led to the development of new large-scale technical processes as well as heralding an almost unimaginable flood of patents and publications. Years later the "nickel effect" initiated a further development which can be described as the chemistry of "naked nickel"[3]. This in turn led to the pure π-allyl transition metal systems[4] of which bis(π-allyl)nickel[5] has become the prototype.

In the following article the opportunity is taken to report on some new results from the Mülheim Institute concerning the chemistry of nickel complexes. Initially, however, it seems relevant to describe the original observations which led, twenty years ago, to the "nickel effect", and then to answer the question: What do we know about it today?

Ziegler and *Gellert*[6, 1c] observed that triethylaluminum reacts at 100 °C with ethylene under pressure to give trialkylaluminum compounds whose alkyl chains may have molecular weights of *ca.* 3000 in extreme cases. In other words, higher trialkylaluminum compounds can be prepared in an organometallic synthesis involving the repeated addition of the Al—C bond to the C=C bond of the ethylene molecule. Hydrolysis of these higher alkyls produces wax-like *n*-paraffins whose molecular weights were found to depend upon the ratio of triethylaluminum to ethylene.

An extended series of experiments always led to more or less the same result until unexpectedly one experiment, although carried out as usual, produced almost exclusively

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butene—the dimer of ethylene. A systematic search for the component responsible for this effect, although initially fruitless, finally revealed that traces of nickel salts, in particular bis(2,4-pentanedionato)nickel [$Ni(acac)_2$], present as cocatalysts in the triethylaluminum caused chain cleavage after each insertion step[1]. In the original experiment a V2A autoclave had been cleaned with sulfuric acid and as a result traces of nickel salts had been left behind[1b].

Subsequently we learnt how to generate a highly active, stable cocatalyst and the following recipe was developed on a purely empirical basis[7]:

$Ni(acac)_2$ is dissolved in xylene, phenyl acetylene (1:30) added, and the mixture treated as carefully as possible with $(C_2H_5)_2AlOC_2H_5$. The actual catalyst—triethylaluminum—is then added to the resulting orange-red solution. Using this system it is possible to convert ethylene into butene in over 90% yield.

At that time hardly anything was known about π-complexes and it was therefore assumed that the orange-red solution contained colloidal nickel stabilized by phenylacetylene[1,7]. The basis of the principle which we developed later for the synthesis of transition metal complexes by reduction of transition metal compounds by alkylmetal compounds in the presence of molecules capable of functioning as ligands[8] is already latent in the above procedure. It is also a curious coincidence that the cocatalyst in this procedure is itself able to catalyze the cyclooligomerization of butadiene to cyclooctadiene and cyclododecatriene[9]. Such is the early history.

Although the "nickel effect" has had such important consequences, the mechanism of the reaction has received relatively little attention, and even in the face of an extensive organic chemistry of nickel, conclusive mechanistic evidence is still lacking today. The following discussion, however, should contribute substantially towards an explanation.

2. Reduction of Bis(pentanedionato)nickel by Trialkylaluminum[10]

2.1. Reduction by Trimethylaluminum

When a solution of bis(pentanedionato)nickel [$Ni(acac)_2$] *(1)* in toluene is treated with $Al(CH_3)_3$ *(2)* elemental nickel is rapidly deposited, even at temperatures below −100 °C, and methane and ethane are liberated. The overall reaction is described approximately by:

$$\underset{(1)}{Ni(acac)_2} + 2\ \underset{(2)}{Al(CH_3)_3} \rightarrow Ni + [0.25\ C_2H_6 + 0.5\ (CH_3)_2Alacac] + [1.5\ CH_4 + 1.5\ H_3C{-}\underset{\displaystyle -CH_2}{\overset{\displaystyle |}{Alacac}}]$$

Experiments in D_8-toluene show that the CH_3 radicals, presumably produced by the decomposition of an intermediate $Ni(CH_3)_2$ species, preferentially abstract H atoms from the $Al(CH_3)_3$ since practically no CH_3D is formed. The $Al{-}CH_2$ group could not be detected as $Al{-}CH_2{-}Al$, in contrast to the results obtained, for example, by *Sinn et al.*[11] with the $(C_5H_5)_2TiCl_2$ and $Al(CH_3)_3$ systems. The use of $Al(CD_3)_3$ in toluene produces a mixture of CD_3H and CD_4 in the ratio 1.5:1, apparently as the result of an isotope effect, *i.e.* the H atoms of the toluene are somewhat more easily abstracted than the D atoms of $Al(CD_3)_3$. Experiments carried out in the continuous flow cell of an ESR spectrometer demonstrate that free radicals are not formed in measurable concentrations.

It has been possible to isolate a stable derivative of dimethylnickel by working in the presence of α,α′-bipyridyl; the complex bpy·$Ni(CH_3)_2$ *(3)*, recrystallizable from boiling benzene, is obtained[12]. This complex is particularly suitable for studying the decomposition of $Ni(CH_3)_2$ since the bipyridyl can be removed, for example, by treatment with Lewis acids at room temperature.

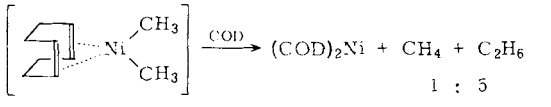
$$\underset{(3)}{bpy\ Ni(CH_3)_2} \xrightarrow{2\ Al(CH_3)_3} \underset{(4)}{bpy \cdot 2\ Al(CH_3)_3} + Ni + CH_4 + C_2H_6 \quad (5:1)$$

$$\underset{(3)}{bpy\ Ni(CH_3)_2} \xrightarrow{2\ BF_3} bpy \cdot 2\ BF_3 + Ni + CH_4 + C_2H_6 \quad (1:7)$$

The composition of the gas is markedly dependent upon the Lewis acid, and only the extreme cases are shown above. However, from a series of experiments using $Al(CH_3)_3$, $Al(CH_3)_2Cl$, $AlCH_3Cl_2$, $AlCl_3$, and BF_3 it is possible to follow the change in the $CH_4:C_2H_6$ ratio from 5:1 to 1:7.

These experiments also demonstrate that the H atom is abstracted preferentially from the organoaluminum component. If the Lewis acid contains no H atoms then mainly dimerization occurs. The same behavior is also observed on addition of the chelating ligand 1,5-cyclooctadiene (COD).

$$\underset{(3)}{bpy \cdot Ni(CH_3)_2} + \underset{(2)}{2\ Al(CH_3)_3} + COD \rightarrow \underset{(4)}{bpy \cdot 2\ Al(CH_3)_3} +$$

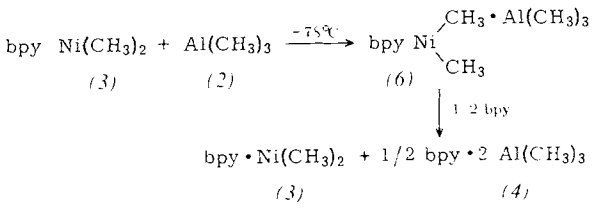


$$\rightarrow (COD)_2Ni + CH_4 + C_2H_6 \quad (1:5)$$

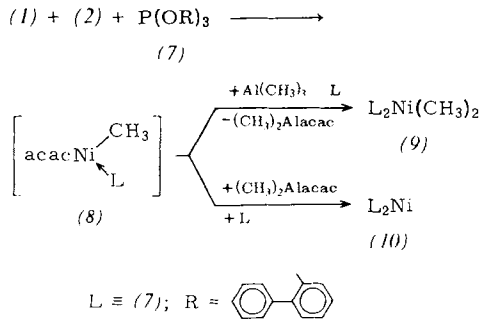
(5)

Apparently the CH_3 groups in complex *(5)* (which has not been isolated) are held in a *cis*-arrangement so that homolysis of the Ni—C bond leads preferentially to coupling. This could be interpreted as indicating that the CH_3 radicals which abstract H atoms result from a linear $Ni(CH_3)_2$ species. It has been possible to isolate a crystalline intermediate *(6)* in the decomposition of *(3)* by *(2)* by working at low temperature.

At higher temperature *(6)* decomposes in the normal manner and may be reconverted into *(3)* by use of excess bipyridyl.



It is relevant to mention the somewhat different behavior observed in the related reaction of *(1)* with *(2)* in the presence of tris(2-biphenylyl) phosphite *(7)* (L) as a function of the concentration of *(2)*[12, 13a].

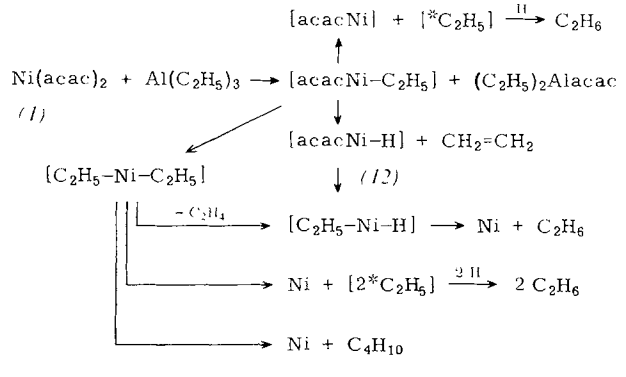


The intermediate *(8)* reacts with excess *(2)* to give the stable complex *(9)*, while an initial ratio of *(1)*:*(2)* of 1:1 leads exclusively to *(10)*. The interaction of *(8)* with the pentanedionate group in $(CH_3)_2Al(acac)$ is clearly important here. When L = tricyclohexylphosphane, *(8)* could be isolated in crystalline form[13b] and its structure determined by X-ray crystallography[13c].

Thus the reduction of the nickel in *(1)* by $Al(CH_3)_3$ is considered to proceed, in general, by homolysis of the Ni—C bond of an intermediate dimethylnickel species. Under certain conditions the CH_3 groups preferentially couple giving ethane.

2.2. Reduction by Triethyl- or Triisobutylaluminum

A somewhat different behavior is observed in the reduction of $Ni(acac)_2$ by alkylaluminum compounds whose alkyl groups have a H atom in a β position to the Al atom:



homolysis giving alkyl radicals, which abstract H atoms, and the dimerization of alkyl groups, are accompanied by a β H elimination to give a Ni—H species and an olefin. Under suitable conditions gas yields of 85—100% can be obtained.

The extent to which the reaction follows a particular direction is dependent upon a number of external factors (purity of $Ni(acac)_2$, hydride content of the $Al(C_2H_5)_3$, solvent, temperature, presence of ligands). The following behavior is typical:

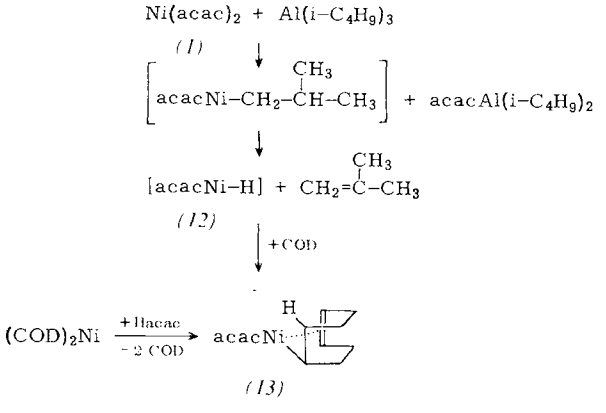
$Ni(acac)_2$ (3 mmol) in toluene (10 ml) at −78 °C, treated with hydride-free $Al(C_2H_5)_3$ (6 mmol), on warming to 20 °C generates ethane (2.5 mmol), ethylene (0.4 mmol), butane (1.5 mmol), and butene (0.1 mmol). Thus the ethyl groups corresponding to the 6 mmol which are used for the reduction of the $Ni(acac)_2$ appear almost quantitatively in this gas mixture.

The main reactions are again H abstraction (ethane) and dimerization (butane), the β elimination (ethylene) appearing to play a less important role.

The reaction of *(1)* with $Al(i\text{-}C_4H_9)_3$ occurs almost exclusively as a β-H elimination without coupling and without radical H abstraction: isobutane and isobutene are produced in an almost exact 1:1 ratio in over 90% yield.

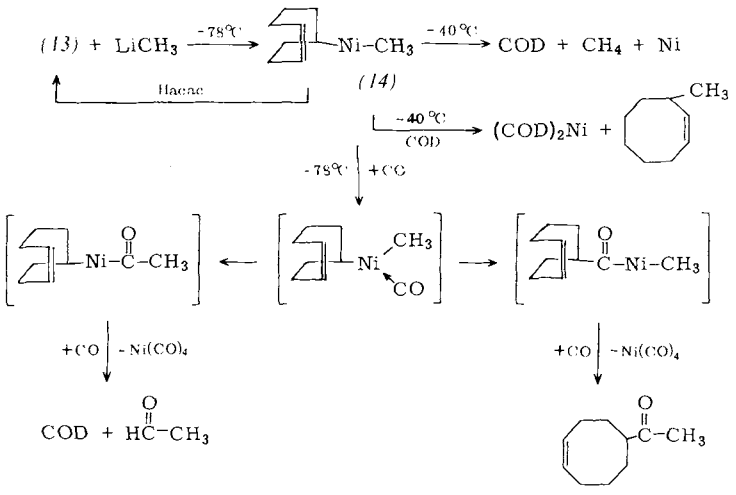
2.3. Trapping of the Intermediate Pentanedionatonickel Hydride

In the reaction scheme shown in Section 2.2, pentanedionatonickel hydride *(12)* is formulated only as a possible intermediate. That it is involved may be indicated by working in the presence of cyclooctadiene:

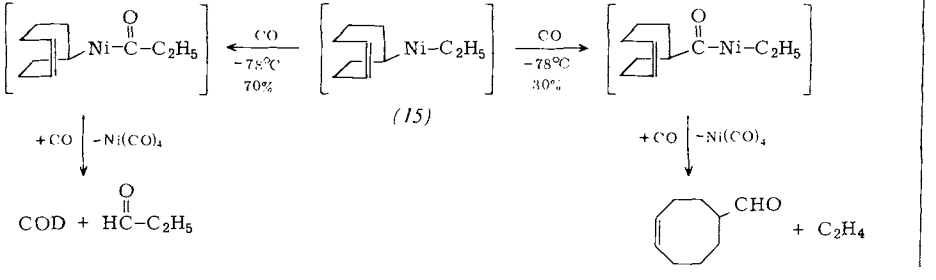


On addition of the Ni—H bond to a C=C bond of 1,5-cyclooctadiene, 4-cyclooctenyl(pentanedionato)nickel *(13)* is produced and can be isolated in crystalline form. We have previously synthesized *(13)* from $(COD)_2Ni$ and 2,4-pentanedione[8] and its structure has been established by an X-ray structural analysis[14]. It is obvious that *(13)* cannot be formed in reactions involving $Al(CH_3)_3$.

(13) can itself be regarded as an intermediate since further reduction in the presence of COD leads to bis(cyclooctadiene)nickel. In this reaction alkyl(4-cyclooctenyl)nickel complexes are involved and the methyl derivative *(14)* has been isolated as a red crystalline solid:



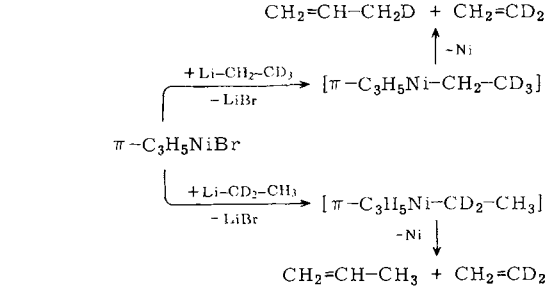
Decomposition of *(14)* occurs by β-H elimination to give COD and CH_4. Decomposition in the presence of COD, however, occurs almost exclusively by coupling [*viz.* bipy·$Ni(CH_3)_2$] and is accompanied by isomerization, since 3-methylcyclooctene and not 5-methylcyclooctene is produced. β-H elimination on the one hand and coupling on the other are even observed in the products resulting from carbonylation. The ethyl compounds *(15)*, corresponding to *(14)*, cannot be isolated but their formation may be indirectly established by investigating the products of carbonylation.



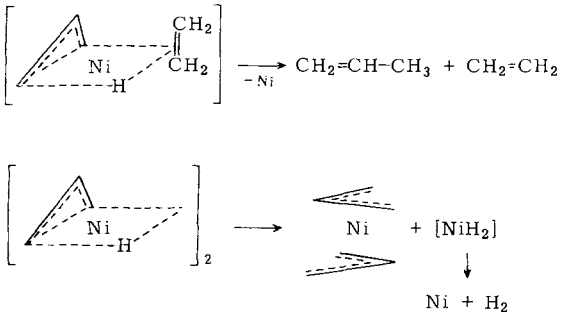
The acyl derivatives obtained from *(15)* react exclusively by β-H elimination.

2.4. A Model for β-H Elimination[15]

We have observed a particularly convincing example of the β-H elimination in the reaction of π-allylnickel bromide with ethyllithium deuterated in either the α- or β positions. At −70 °C the ethyl group is transferred to the nickel to give π-allyl(ethyl)nickel which immediately undergoes a β-H elimination to give ethylene and the unstable π-allylnickel hydride; this, in turn, reacts further by transfer of the hydride atom to the allyl group to generate propene and elemental nickel. The gaseous reaction products (yield >95%) consist of either 3-deuteriopropene and 1,1-dideuterioethylene or of propene and 1,1-dideuterioethylene, depending upon the position of deuteration in the ethyllithium used.



The course of the reaction is apparently influenced by the ethylene generated, since the observed decomposition of the intermediate π-allylnickel hydride complex to propene and nickel only occurs under the conditions described above. In contrast, the reaction of π-allylnickel bromide with NaH·$B(CH_3)_3$[24] is accompanied by disproportionation of the π-allylnickel hydride into essentially pure *trans*-bis(π-allyl)nickel[16] and the unstable NiH_2, which decomposes into nickel and hydrogen. From these results one can conclude that the coupling reaction which leads to propene is the result of the complexation of the ethylene; in the absence of ethylene the dimeric π-allylnickel hydride presumably disproportionates.

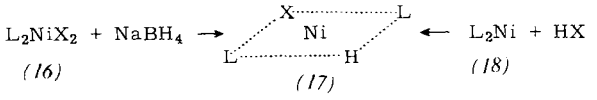


The results described in Sections 2.1 to 2.4 are not only relevant to the nickel-effect but also of general interest, since the same processes are observed in the synthesis of transition metal complexes, in the preparation of catalysts for olefin oligomerization, and also in the catalytic reactions themselves[17] (see, *inter alia* ref. [40]).

3. Stable Nickel Hydrides

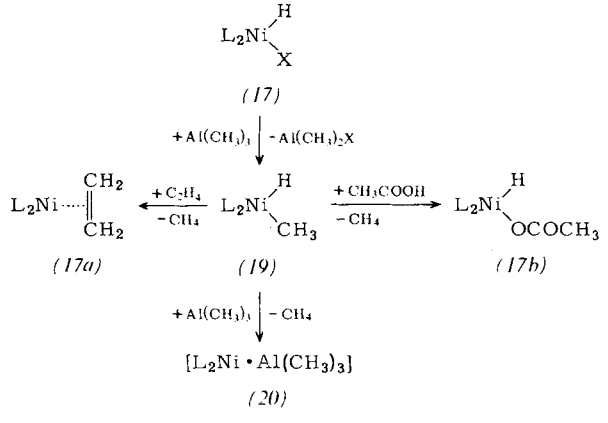
Interest in a possible NiH_2 species in conjunction with the catalytic hydrogenation using nickel catalysts stems from the year 1923[18]. However, more recent results[19] have not supported the early work. A series of carbonylnickel hydrides have been known since 1953 in which several nickel atoms are bridged by CO molecules; however, these complexes are of no relevance here.

The first evidence for the existence of phosphanenickel halide hydrides was obtained in 1959—1960[20] when a high field signal was observed in the ^{1}H-NMR spectrum of a reaction mixture consisting of $(R_3P)_2NiCl_2$ *(16)* and $NaBH_4$ dissolved in THF. A definite compound, however, could not be isolated and ten years elapsed before a complex of the type $(R_3P)_2NiHX$ *(17)* was prepared—practically simultaneously by *Green*[21] and ourselves[22] although by completely different routes: *Green* and *Saito* treated *(16)* with $NaBH_4$ while we prepared *(17)* by the oxidative addition of HX to an L_2Ni-system *(18)*.



L = P(Alkyl)$_3$, P(Cycloalkyl)$_3$
X = Cl, Br, I, $OCOCH_3$, OC_6H_5, 1-Pyrrolyl

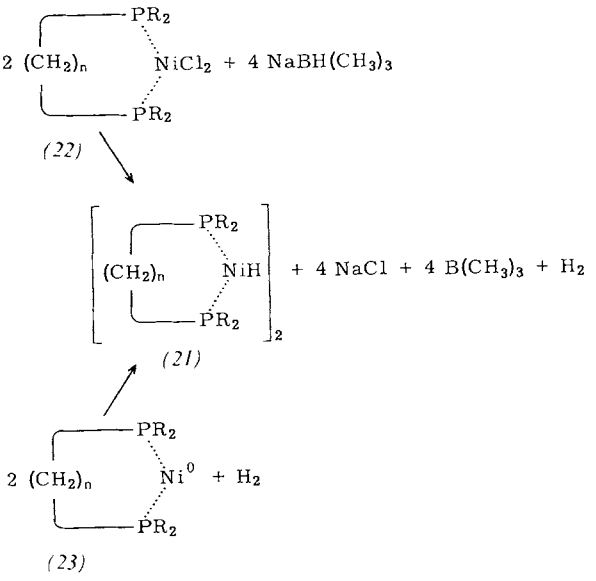
Complexes of type *(17)* are most probably planar with the phosphane ligands in a *trans*-arrangement[*] [L = $P(C_6H_{11})_3$, X = Cl; τ = 34.6 (t, H_{Ni-H}; J_{PH} = 73.5 Hz)]. At least 20 further examples of this type of compound are now known. *(17)* can be viewed as a model for the catalysts described in the preceding sections[17]. Its reactions to give *(17a)*, *(17b)*, and *(20)* are characteristic.



The product *(19)* of the reaction between *(17)* and $Al(CH_3)_3$ is stable at room temperature and releases methane on protonolysis with acetic acid to give *(17b)*[22]. Treatment with ethylene effects a coupling reaction to give methane and an ethylene complex *(17a)*. Compound *(19)* also reacts with $Al(CH_3)_3$, releasing methane, to give the rather indefinite product *(20)*. (Compounds of this type are treated in Section 4.)

Nickel hydrides *(21)* having a remarkable structure[23] are formed when nickel chloride bonded to an oligomethylenebis(phosphane) *(22)* is treated with a toluene solution of $NaBH(CH_3)_3$[24].

The resulting complexes *(21)* are diamagnetic and of unusual stability (*(21a)* does not decompose below 150 °C). The structure of *(21b)* has been determined by X-ray



(a), n = 2; *(b)*, n = 3; *(c)*, n = 4; R = c-C_6H_{11}

crystallography (Fig. 1). It also proved possible to locate the bridging H atoms[25] (Fig. 2).

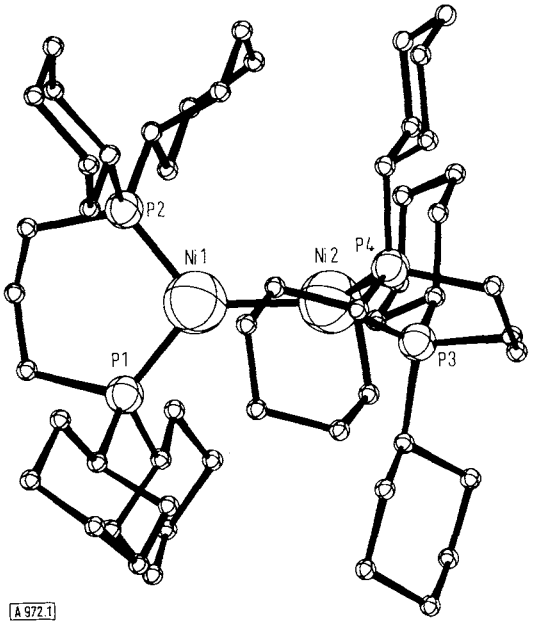


Fig. 1. Crystal structure of di-μ-hydridobis[trimethylenebis(dicyclohexylphosphane)nickel] *(Ni—Ni) (21b)*.

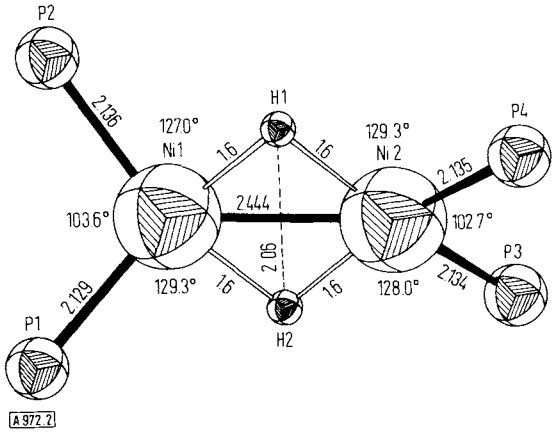
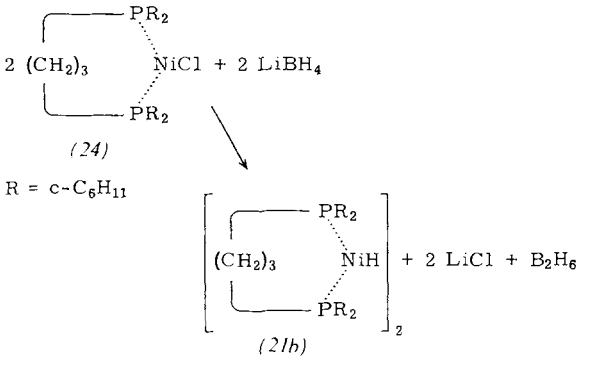


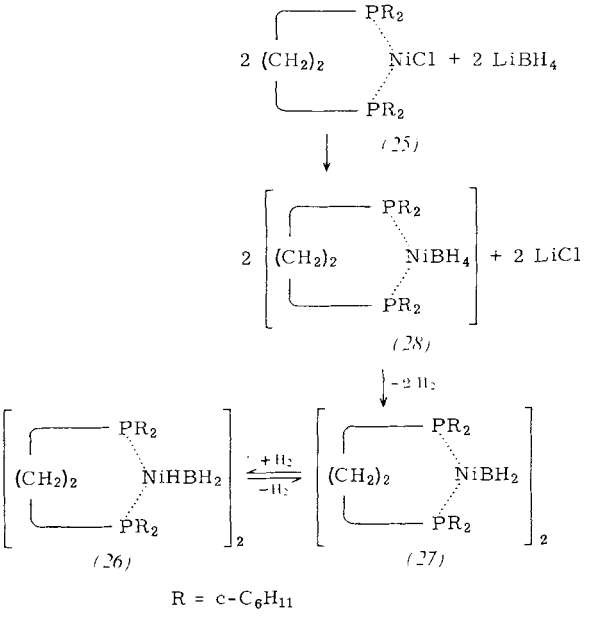
Fig. 2. Arrangement of bridging H atoms in *(21b)*.

[*] An X-ray structural determination of $[i\text{-}(C_3H_7)_3P]_2NiHCl$ confirms this arrangement. Personal communication from *U. A. Gregory* and *B. T. Kilbourn*, quoted by *B. A. Freny* and *I. A. Ibers* in: Transition Metal Hydrides. Dekker, New York 1971, p. 45.

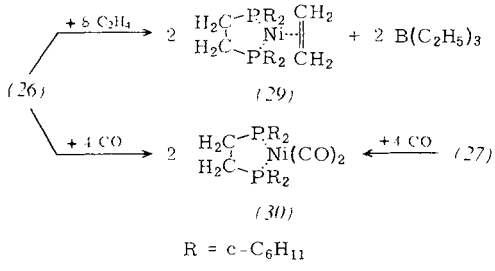
The ^{1}H-NMR spectrum is in full accord with this structure (H_{NiHNi}, $\tau = 21.4$, quintet, $J_{PH} = 23.5$ Hz). Owing to the Ni—Ni bond the nickel(I) hydride *(21b)* is diamagnetic. *(21a)* is also obtained when the bis(phosphane)nickel(0) system *(23a)* is treated with molecular hydrogen. Thus an impressive model is available for the cleavage of the H_2 molecule occurring during catalytic hydrogenations at nickel surfaces. *(21b)* also results from the nickel(I) complex *(24)* and $LiBH_4$.



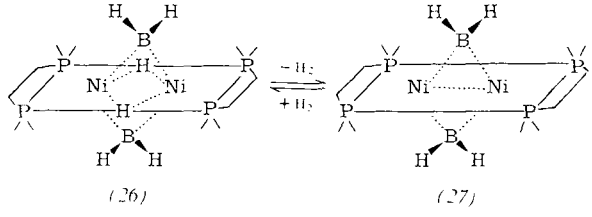
However, if the bridge between the phosphorus atoms consists of only two CH_2 groups *(25)*, then a complex *(26)* can be isolated after reaction with $LiBH_4$.



In the first step *(25)* is postulated to give an unstable $NiBH_4$ system *(28)*[*] from which H_2 is released to give the nickel boron compound *(27)*; this in turn absorbs hydrogen and is converted into *(26)*. The isolated complex *(26)* releases hydrogen to give *(27)* which can also be isolated. This step is reversible, although limited by the gradual decomposition which occurs. *(26)* absorbs ethylene smoothly to give *(29)* and $B(C_2H_5)_3$, while both *(26)* and *(27)* react with CO to give *(30)*, although in neither case could a product containing the BH_3 or BH_2 group be isolated.

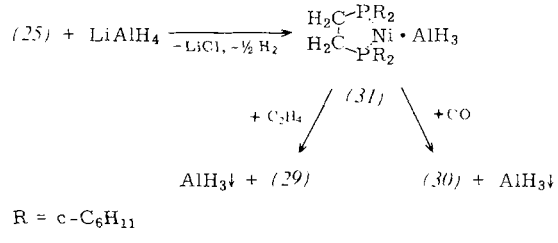


Both *(26)* and *(27)* are diamagnetic and are suggested, by analogy with *(21b)*, to be dimeric.



The IR-spectrum of *(26)* contains bands attributable to both terminal and bridging H atoms.

The corresponding AlH_3 derivative *(31)* is presumed also to belong to the same class of compounds and may be prepared in an analogous manner by treating *(25)* with $LiAlH_4$.



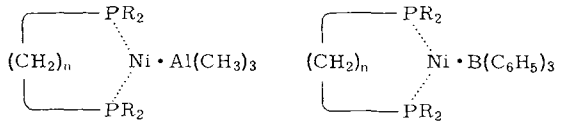
Although AlH_3 is not normally monomeric it is complexed in this form to the bis(phosphane)nickel system of *(31)* from which it may be eliminated by treatment with ethylene or CO, simultaneously polymerizing. The reaction of *(31)* with ethylene differs from that of *(26)*; although *(29)* is formed, no $Al(C_2H_5)_3$, corresponding to the formation of $B(C_2H_5)_3$, is produced.

4. Interaction of Nickel(0) with Organometallic Compounds and Lewis Acids

It has repeatedly been observed that solutions of nickel(0) with or without donor ligands, are stabilized by aluminum alkyls. However, in most cases it has not proved possible to isolate any well defined products. The stabilization could be the result of Lewis acid—Lewis base interaction in which the nickel(0) is regarded as a Lewis base. However, the generation of multicenter bonds between the nickel(0) and the metal alkyl seems to be of more significance.

[*] *M. L. H. Green, H. Munakata,* and *T. Saito* have described a stable $L_2Ni(H_2BH_2)$ system; J. Chem. Soc. *A 1971*, 469.

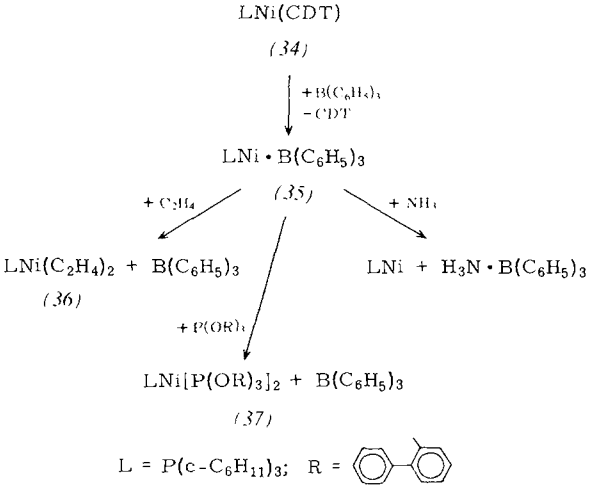
The incompletely characterized compound *(20)* mentioned in Section 3 can be viewed as an example of this type of interaction. Other isolable complexes include a 1:1 adduct *(32)* of the bis(phosphane)nickel(0) complex *(23)* and $Al(CH_3)_3$, as well as the complexes *(33a)* and *(33b)*.



(32) *(33)*

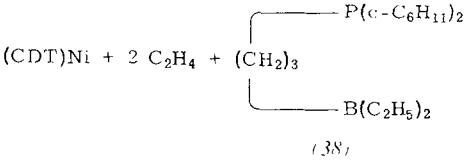
(a), n = 2; *(b)*, n = 3; R = c-C_6H_{11}

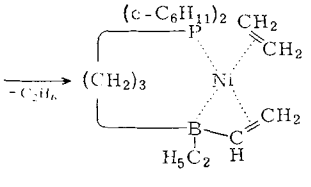
It is not essential for adduct formation that the nickel atom be bonded to a bis(phosphane) system, and particularly interesting is the displacement of the 1,5,9-cyclododecatriene (CDT) from the 1:1 complex *(34)* (formed by reaction of cyclododecatrienenickel with P(c-C_6H_{11})$_3$) by reaction with $B(C_6H_5)_3$. The resulting product *(35)* is a complex of tricyclohexylphosphanenickel and triphenylborane.



(35) can be cleaved both by those ligands which bond preferentially to nickel(0) as well as by Lewis bases *e.g.* ethylene, tri-(2-biphenylyl)phosphite and ammonia.

Complexes *(20)*, *(21)*, *(27)*, *(31)*, *(32)*, and *(33)* are either of low stability or are readily cleaved by ligands such as phosphanes or olefins. In the hope that stable





(39)

complexes could be prepared if the Lewis acid were part of a chelating ligand bonded to the nickel, borylphosphanes of type *(38)* were synthesized[27] and allowed to react with (CDT)Ni and ethylene: displacement of the CDT from the nickel by the borylphosphane *(38)* and ethylene occurred.

An X-ray structural analysis[28] of the crystalline complex *(39)* (Fig. 3) as well as its NMR spectrum show that upon complexation an alteration in *(38)* has occurred: an ethyl group has been exchanged for a vinyl group which is complexed to the nickel. The B—Ni distance of ≈ 2.5 Å does not allow a final decision to be made as to whether a bonding situation exists between the boron and nickel.

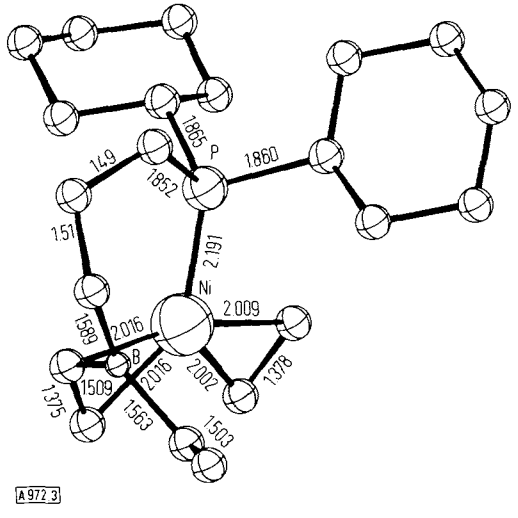
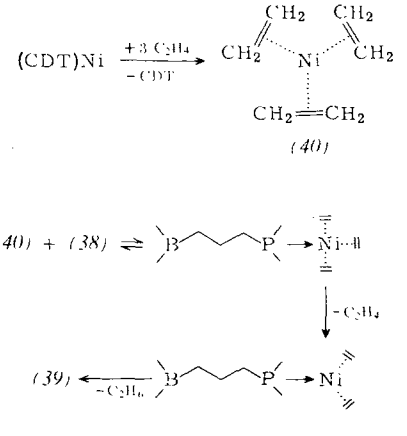


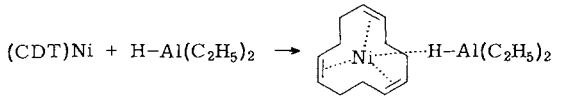
Fig. 3. Crystal structure of ethylene[ethyl(vinyl)borylpropyldicyclohexylphosphane]nickel(0) *(39)*.

The intermediates involved in the formation of this complex and in particular the process leading to the vinyl group remain unknown. Almost certainly the first step is the displacement of the CDT by ethylene, since (CDT)Ni does not react with *(38)* in the absence of ethylene. Tris(ethylene)nickel(0) *(40)*, first discovered in this experiment[29], is formed and reacts further in a synchronous process



in which an H atom of a complexed ethylene molecule is transferred to the *B*-ethyl group, liberating ethane and generating the *B*-vinyl system.

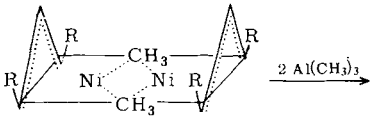
At the beginning of this section we mentioned the stabilizing effect of aluminum alkyls upon solutions containing nickel(0) as well as the fact that well defined products cannot, in general, be isolated. In this context it is of interest that a crystalline compound *(41)*[27] can be prepared by reacting (CDT)Ni and dialkylaluminum hydride (1:1) at −78 °C. Protonolysis of the decomposition product [*(41)* decomposes above −60 °C] gives a mixture of cyclododecadiene, cyclododecene, and cyclododecane, in addition to cyclododecatriene (CDT), showing that addition of the Al—H bonds to the C=C bonds has occurred. The ^{1}H-NMR spectrum of *(41)* indicates that the hydridic hydrogen atom of the diethylaluminum hydride is bonded to the fourth coordination position of the nickel (Al—*H*—Ni, τ = 15.2, s; free $(C_2H_5)_2AlH$, τ = 7.36).



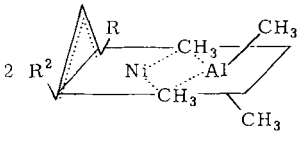
(41)

With ether *(41)* forms a 1:1 adduct, in contrast to free $(C_2H_5)_2AlH$ which is highly associated. This example illustrates that multicenter bonds of this type need to be considered in any discussion on the interaction of organoaluminum compounds with nickel complexes.

Multicenter bonds between like species have been conclusively demonstrated in the nickel(I) hydride *(21b)* as well as in the dimer of π-allyl(methyl)nickel *(42)*[30]. This last compound even shows a molecular peak in the mass spectrum corresponding to a dimer, *i.e.* the Ni—CH_3—Ni group is relatively stable. Apparently the Ni—CH_3—Al bond is of even greater stability since on reaction of *(42)* or *(43)* with $Al(CH_3)_3$ *(2)* monomerization occurs to give the 1:1 adduct *(44)* or *(45)*.



(42), R = H
(43), R = CH_3



(44), R = H
(45), R = CH_3

The ^{1}H-NMR spectrum of *(44)* at low temperature consists of three signals (2:1:1) for the CH_3 protons. The signal having an intensity of 2 is assigned to the protons of the bridging CH_3 groups and the remaining two to the terminal CH_3 groups. In the case of the more stable complex *(45)* it is possible to show from the ^{1}H-NMR spectrum that the bridging and terminal CH_3 groups are rapidly exchanging positions at higher temperatures[30b].

The formation of such multicenter bonds is not limited to the nickel(0)-aluminum hydride or -alkylaluminum systems and recent investigations[31, 26] have shown that the alkyl and aryl groups of organolithium compounds can also bond to nickel(0). Phenyllithium reacts with (CDT)Ni to give a 1:1 adduct in which the phenyl group is presumed to occupy the fourth coordination position at the nickel, thereby forming a Ni—C—Li bridge. The existence of such a bridge in $[(LiC_6H_5)_3Ni]_2N_2 \cdot 2O(C_2H_5)_2$ (which contains π-bonded dinitrogen[32]) has been established by an X-ray structural analysis[33].

Ethyllithium and ethylene react with bis(cyclooctadiene)nickel at −30 °C with complete displacement of the olefin molecules: at low temperatures a complex *(46)* may be isolated in which the ethyl groups apparently interact with the nickel[26].

$$(COD)_2Ni + C_2H_4 + 2LiC_2H_5 \xrightarrow[-2COD]{+O(C_2H_5)_2} (LiC_2H_5)_2Ni \cdot C_2H_4 \cdot O(C_2H_5)_2$$

(46)

If the reaction is carried out at 20 °C without an excess of ethylene, then *(47)* is formed almost quantitatively[26].

$$(COD)_2Ni + 3LiC_2H_5 \rightarrow (LiH)_3Ni \cdot C_2H_4 + 2COD + 2C_2H_4$$

(47)

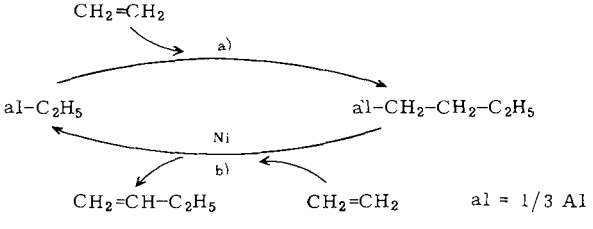
Complex *(47)* has a certain similarity with the well known complex $K_4[Ni(C{\equiv}CH)_4]$[34], although in the former case the four coordination positions around the nickel(0) are occupied by three hydride ions and an ethylene molecule.

Of special interest is the coordination of ethyllithium to nickel(0): under the influence of the nickel, cleavage into lithium hydride and ethylene occurs at room temperature (in the absence of nickel a temperature of at least 100 °C is necessary). In this case the nickel facilitates, particularly effectively, stoichiometric β-H elimination in an alkyl compound of a main-group metal.

5. Mechanism of the "Nickel Effect"

5.1. Former Concepts

The "nickel effect" was discovered in 1955 during a study of the insertion of ethylene into $Al(C_2H_5)_3$ (see Section 1). The catalytic cycle in which ethylene is dimerized can be divided into an insertion step (a) and a displacement step (b) as illustrated schematically below:



Only step b) is influenced by the nickel and can be carried out, independently of the insertion reaction, with any trialkylaluminum.

$$Al(CH_2{-}CH_2{-}R)_3 + 3\,CH_2{=}CH_2 \xrightarrow{Ni} Al(C_2H_5)_3 + 3\,CH_2{=}CH{-}R$$

The mechanism of the nickel-catalyzed displacement reaction has been considered by four groups of authors.

Ziegler et al. expressed themselves as quoted below:[7] "The activity of the (colloidal) nickel is still not understood. It could be that it catalyzes a genuine displacement (in a bimolecular collision) of the type

$$R'al + olefin^{II} \rightarrow R^{II}al + olefin^{I}\ [*]$$

in which the dialkylaluminum hydride does not function as an intermediate".

Eisch and *Foxton*[35] later suggested the following mechanism without actually having investigated the reaction experimentally[**]:

$$(C_4H_9)_3Al + NiZ_2 \rightleftharpoons C_4H_9NiZ + (C_4H_9)_2AlZ$$

$$C_4H_9NiZ \rightleftharpoons HNiZ + C_4H_8$$

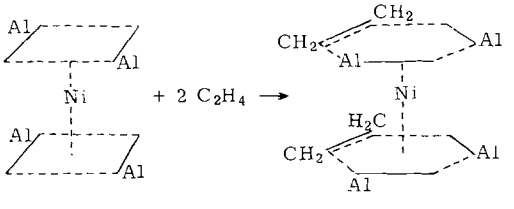
$$C_2H_4 + HNiZ \rightleftharpoons CH_2{=}CH_2 \rightleftharpoons H_2C{-}CH_2$$

(Ni, H, Z; ZNi, H)

$$H_2C{-}CH_2 + (C_4H_9)_3Al \rightleftharpoons H_2C{-}CH_2 + C_4H_9NiZ$$

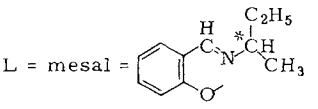
(ZNi, H; $(C_4H_9)_2Al$, H)

Lucas[36] has discussed a π-complex of the following type:



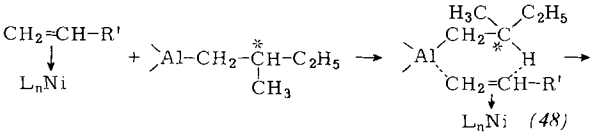
Experimental evidence for the existence of such complexes was not presented.

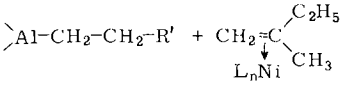
The most extensive study has been made by *Pino et al.*[37]. They were able to show that the use of nickel(II) compounds containing optically active groups induces optical activity during the displacement reaction. It was concluded that at least one optically active group remains bonded to the catalytically active nickel. This conclusion is supported by the observation that the original nickel compound could be regenerated by protonolysis after the reaction with alkylaluminum[***]. In addition, the participation of HNiZ intermediates could be largely eliminated. The displacement reaction can be summarized as shown below[****]:

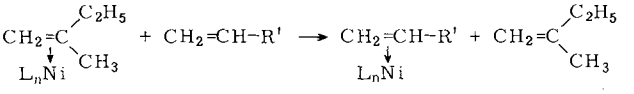


$$Ni(mesal)_2 + xAlR_3 \rightarrow L_nNi$$

$$L_nNi + CH_2{=}CH{-}R' \rightarrow CH_2{=}CH{-}R'$$
$$\downarrow$$
$$L_nNi$$







The complex *(48)* formed from L_nNi, the olefin, and the alkylaluminum is regarded as being of central importance.

5.2. Recent Experimental Results[27]

Before considering the various mechanistic suggestions we shall present some recent experimental results which enable the further discussion to be placed on a more certain basis.

The extremely sensitive tris(ethylene)nickel *(40)*[29], obtained by treating (CDT)Ni with ethylene at 0 °C, is stabilized significantly by $Al(C_2H_5)_3$ without any reaction being observed; however, when perdeuterioethylene is used a deuterated triethylaluminum results. If $Al(C_4H_9)_3$ is reacted instead of $Al(C_2H_5)_3$ in a ratio of 1:1 then the following conversion occurs instantaneously and almost quantitatively:

$$Ni(C_2H_4)_3 + Al(C_4H_9)_3 \rightarrow 3\,C_4H_8 + Al(C_2H_5)_3 + Ni$$
(40)

This is the first example in which a well defined nickel(0) complex takes part in a stoichiometric displacement reaction with a trialkylaluminum. The ethylene molecule causing the displacement is that originally bonded to nickel(0) which, however, does not prove that the reacting ethylene is in a complexed state. The reaction is catalytic if carried out in the presence of excess ethylene and $Al(C_4H_9)_3$. Various other nickel(0) complexes catalyze the reaction of ethylene with trialkylaluminum compounds in a manner similar to *(40)* and high catalytic activity is observed

[*] al = 1/3 Al.

[**] The original scheme is applied here, in simplified form, to the $Al(C_4H_9)_3{-}C_2H_4$ system.

[***] Protonolysis in the presence of atmospheric oxygen produces nickel(II) which reacts immediately with the liberated phenol *e.g.* H mesal, to give the original nickel(II) compound.

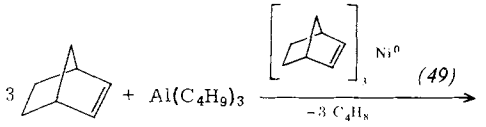
[****] Original formulation.

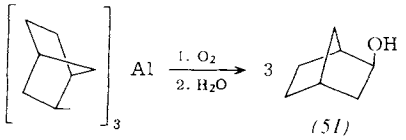
for those complexes in which the nickel atom is associated either solely with olefinic ligands or at the most with a single phosphane-like ligand. If more than one coordination position is blocked by a phosphane then the activity of the catalyst sinks sharply.

Unexpectedly, the nickel(0) also loses its activity if, for example, tris(ethylene)nickel(0) *(40)* is treated with diethylaluminum hydride. The origin of this behavior is still unknown.

The following observations are also of relevance to the discussion of the "nickel effect":

Bicycloheptene and $Al(C_4H_9)_3$ do not react to any significant extent at 20°C; however, upon addition of a catalytic amount of tris(bicycloheptene)nickel(0) *(49)*[38] butene is released and the organoaluminum compound *(50)* is formed. The main product of the air oxidation of *(50)* and subsequent hydrolysis is *exo*-norbornanol *(51)*[41].





(50) *(51)*

The X-ray structural analysis of *(49)*[39] shows that the nickel atom is attached *exo* to the double bond of the bicycloheptene molecule (Fig. 4).

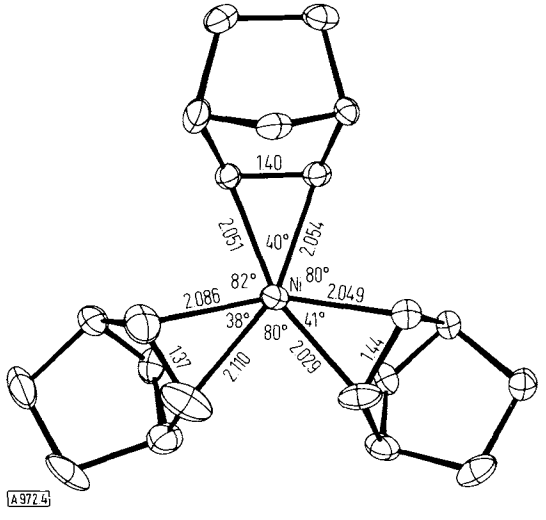
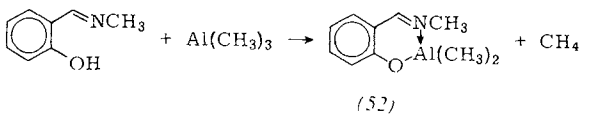


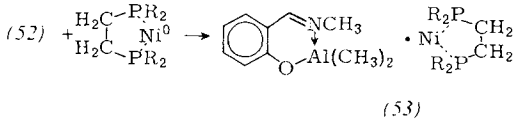
Fig. 4. Crystal structure of tris(bicycloheptene)nickel(0) *(49)*.

Finally, it has been possible to synthesize a model compound *(53)* relevant to the mechanism proposed by *Pino*.

Compound *(53)* is crystalline and stable up to 100°C. Its structure is not known with complete certainty but it can be assumed that the C=N bond is complexed to the nickel atom.



(52)



(53)

R = c-C_6H_{11}

5.3. Discussion of the Mechanism

Although colloidal nickel cannot be completely ruled out as the active species, the reactions of $Al(C_4H_9)_3$ with both tris(ethylene)nickel(0) *(40)* and tris(bicycloheptene)-nickel(0) *(49)* demonstrate that complexes of nickel(0) actively promote the "nickel effect". Diethylaluminum hydride can be discounted as an intermediate since it even functions as a catalyst poison.

The investigations of *Pino et al.* have effectively eliminated the possible intermediacy of an HNiZ species (Z = appropriate ligand). In addition, all experiments show that nickel compounds, particularly at higher temperatures, are quantitatively reduced by trialkylaluminum compounds to nickel(0), *i.e.* the original anions bonded to the nickel are transferred to the aluminum.

This result is in conflict with *Pino*'s assumption that the L_nNi system (L = mesal) is responsible for the induced optical activity. The model compound *(53)* shows that nickel(0) is able to form complexes with compound *(52)*, and the slight induction of optical activity observed can be attributed to complexes of this type.

Although the π-complexes formulated by *Lucas* are not based upon experimental evidence, they nevertheless come closest to the mechanism suggested below since they imply an interaction between the nickel, the olefin, and the trialkylaluminum.

The ability of nickel(0) to complex with olefins has been established for a whole series of examples, and in the context of this article tris(ethylene)nickel(0) *(40)* and tris-(bicycloheptene)nickel(0) *(49)* are particularly relevant examples. The interaction of nickel atoms with alkyls and hydrides of main group metals to form multicenter bonds has also been established in a number of cases [*e.g. (41)*, *(44)*, *(45)*, *(46)*, $[(LiC_6H_5)_3Ni]_2N_2 \cdot [O(C_2H_5)_2]_2$].

The stereochemical course of the reaction between bicycloheptene and $Al(C_4H_9)_3$ in the presence of tris(bicycloheptene)nickel(0) *(49)* shows that tributylaluminum attacks the double bond from the same side as that to which the nickel atom is complexed, and, since no reaction is observed in the absence of nickel, it can be assumed that complexation is a necessary step.

Based upon these results and deductions we propose the following mechanism for the nickel-catalyzed displacement reaction, *i.e.* for the "nickel effect":

The nickel(II) compound introduced as the catalytic component is reduced by the trialkylaluminum, generating nickel(0) which then reacts with the olefins present in

the reaction mixture to form an olefin complex, *e. g.* tris(ethylene)nickel(0) *(40)*. A multicenter bond is formed between the nickel(0) complex and the trialkylaluminum in which the α-C atom of the trialkylaluminum bridges the nickel and aluminum atoms. It can be seen from models that in an arrangement of this sort the C atoms of the complexed olefinic double bond, as well as a β-H atom of the alkyl group, closely approach the Al atom, thereby permitting an electrocyclic reorganization process (Fig. 5).

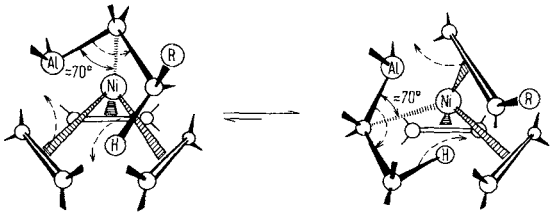


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Fig. 5. Reaction of tris(ethylene)nickel(0) *(40)* with tributylaluminum. $R = C_2H_5$.

The equilibrium shown in Figure 5 is known from experience to lie to the right—this is supported, for example, by the almost quantitative reaction of $Ni(C_2H_4)_3$ *(40)* with $Al(C_4H_9)_3$ which we have already discussed. The driving force for the reaction can be viewed as the energetically favored formation of butene from ethylene. The difference in the heat of hydrogenation is 3 kcal/mol, and it is possible that the energy of association of $Al(C_2H_5)_3$ is slightly higher than that of $Al(C_4H_9)_3$, which would also favor the reaction.

According to the present state of our knowledge the "nickel effect" is seen to result from complexation of ethylene to nickel(0) with simultaneous formation of multicenter bonds between the nickel(0) and the trialkylaluminum.

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Asymmetric Syntheses with the Aid of Homogeneous Transition-Metal Catalysts

By Borislav Bogdanović
Based upon the work of Borislav Bogdanović, Biserka Henc, Arnold Lösler, Burkhard Meister, Horst Pauling, and Günther Wilke[*]

In Memory of Karl Ziegler

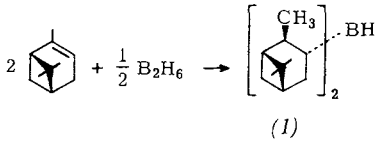
The progress made in the field of homogeneous catalysis during the last five to six years has led, *inter alia*, to the development of highly selective catalysts for asymmetric syntheses. Homogeneous asymmetric hydrogenation, using well defined transition metal catalysts, may be achieved with optical yields of 85 to 90% or more. Catalytic reactions, in which the chiral centers are generated by C—C bond formation, can result in optical yields of 70 to 80%. The hydrogenation catalysts consist primarily of rhodium(I) complexes containing "Horner phosphanes", phosphanes with chiral C atoms, or optically active amides. Catalysts which induce optical activity through the formation of C—C bonds have been developed from π-allylnickel halides, Lewis acids, and phosphanes containing chiral C atoms. The results obtained signify a breakthrough in an area of catalysis previously restricted to syntheses involving enzymes.

1. Introduction

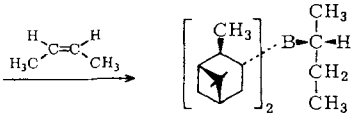
In 1848 *Pasteur*[1] succeeded in effecting the first separation of the two enantiomeric forms of the chiral compound, sodium ammonium tartrate. However, the preparation at will of optically active compounds of high optical purity[****] still remains a challenging problem waiting for a satisfactory solution.

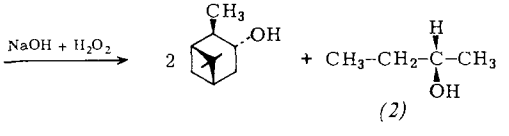
When achiral reactants are used in normal chemical synthesis the products are obtained only in the racemic form. Although racemic mixtures may sometimes be conveniently separated (*e.g.* the technical synthesis of lysine[4]), most separation methods[3] are relatively difficult, requiring large quantities of optically active reagents in relation to the yield of the optically active product obtained.

It is significantly more elegant to set out to prepare optically active compounds more directly with the aid of optically active reagents[5]. A particularly impressive asymmetric hydroboration has been reported by *H. C. Brown et al.*[6]: diisopinocampheylborane *(1)*, obtained by addition of diborane to α-pinene, reacts with 1,2-disubstituted olefins such as *cis*-2-butene to give a new chiral center. Oxidation



(1)





(2)

of the B—C bond, followed by hydrolysis, leads to the secondary alcohol *(2)* in an optical yield of *ca.* 90%. However, it should be noted that at least two moles of the optically active reagent—in this case α-pinene—are required to produce each mole of optically active alcohol *(2)*.

Only those systems involving enzymes[7] are able to convert optically inactive starting materials into optically active compounds of practically 100% optical purity without the help of large quantities of optically active reagents.

Understandably, much effort has been expended in attempts to develop asymmetric catalysts modeled on enzyme systems in the hope that with such systems it would be possible to synthesize optically active substances at will and independently of nature. Until recently such

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[****] *The optical purity* (*O. P.*) is defined as the specific rotation [α] of a substance divided by the specific rotation [*A*] of the pure enantiomer. It is expressed as a percentage:

$$O.P.\,[\%] = \frac{[\alpha]}{[A]} \times 100$$

The value obtained for the optical purity is equivalent to that found for the *enantiomer purity*, which is a measure of the excess of one enantiomer over the other:

$$\text{enantiomer purity}\,[\%] = \frac{F_+ - F_-}{F_+ + F_-} \times 100$$

F_+ and F_- represent the mole fractions of the dextro- and levorotating enantiomers, respectively [2].

The optical yield [%] obtained in an asymmetric synthesis is defined as the optical purity of a reaction product multiplied by 100 and divided by the optical purity of the optically active reactant or catalyst used in the synthesis.

attempts were relatively unsuccessful, but in 1956 *Akabori, Sakurai, Izumi,* and *Fujii*[8-10] succeeded in effecting the asymmetric hydrogenation of various oxime and oxazolone derivatives: optical yields of up to 35%[*] were obtained using a heterogeneous catalyst consisting of metallic palladium drawn out on silk. (Progress in the field of heterogeneous asymmetric hydrogenation is described in reference[11].) The first experiments in which the polymerization of optically inactive monomers were asymmetrically induced using optically active organometallic or Ziegler catalysts were described early in the last decade by *G. Natta et al.*[13]. However, in all these cases the optical yields remained low (6—7%).

Since 1968 cases of catalytically induced asymmetric hydrogenation in the homogeneous phase have been reported; catalysts for these reactions include rhodium complexes containing ligands such as "Horner phosphanes"[**], phosphanes with chiral C-atoms, or optically active amides.

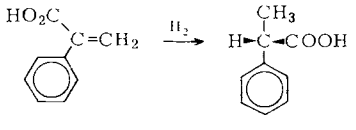
In the catalytic asymmetric hydrogenation reactions the chiral centers are generated during the formation of C—H bonds. However, since 1966 organonickel catalysts containing phosphane ligands incorporating chiral C atoms have been developed here in the Mülheim Institute, and these catalyze asymmetric syntheses in which the chiral center is formed through the linkage of C atoms.

In the following article, a brief review of the developments made in the area of asymmetric hydrogenation is followed by an account of the present status of catalytic asymmetric synthesis involving C—C bond formation.

2. Catalytic Asymmetric Hydrogenation in the Homogeneous Phase

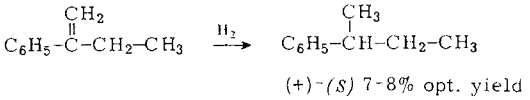
The basis for the development of homogeneous asymmetric hydrogenation catalysts was laid, on the one hand, by the discovery of the versatile rhodium hydrogenation catalysts of the type $Rh(PR_3)_3X$ (X = halogen) by *Wilkinson et al.*[14], and, on the other, by the synthesis of the first optically active phosphanes to contain chiral phosphorus atoms by *Horner et al.*[15]. (The preparation of Horner phosphanes is also described in references[16-18].)

In 1968 two groups of workers, *Knowles* and *Sabacky*[19a], and *Horner, Siegel,* and *Büthe*[20], almost simultaneously reported the first asymmetric homogeneous hydrogenations of optically inactive compounds. The Monsanto group[19a] (see also references[19b, 19c]) prepared the catalyst from the rhodium complexes RhL_3Cl_3 (L = optically active phosphane) by treatment with hydrogen (20 atm) in benzene-ethanol solution in the presence of triethylamine. Using (−)-(*R*)-methyl(phenyl)propylphosphane it was possible to convert atropic acid into (+)-(*S*)-hydratropic acid in an optical yield of 15%.



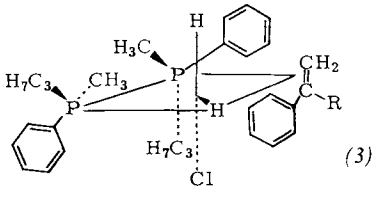
(+)-(*S*) 15% opt. yield

Horner et al.[20b], using a catalyst prepared *in situ* from $[Rh(1,5\text{-hexadiene})Cl]_2$ and (+)-(*S*)-methyl(phenyl)propylphosphane in benzene, effected several hydrogenations including the conversion of α-ethylstyrene to (+)-(*S*)-2-phenylbutane at normal pressure. Optical yields of 7—8% were obtained.



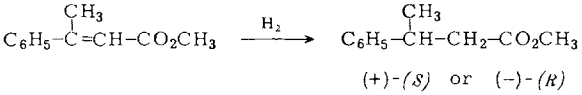
(+)-(*S*) 7-8% opt. yield

The authors attempted to correlate the configuration of the optically active product with that of the optically active phosphane involved using *(3)* (R = *e.g.* C_2H_5, OCH_3) as a model of the catalyst[20b].



(3)

In 1969 *Abley* and *McQuillin*[21] reported the first asymmetric hydrogenation reaction to proceed with an optical yield of over 50%. Methyl β-methylcinnamate was hydrogenated to methyl 3-phenylbutyrate using a catalyst system prepared by reducing $RhCl_3(py)_3$ (py = pyridine) with $NaBH_4$ in *solvents* such as (+)- or (−)-(*N*-1-phenylethyl)-formamide, or other optically active amides.



(+)-(*S*) or (−)-(*R*)
54% opt. yield

Later in this work[22] the catalyst was prepared in ethyl digol[***] to which only 5% (+)-*N*-(1-phenylethyl)formamide had been added (instead of in the pure optically active *N*-(1-phenylethyl)formamide), and the same asymmetric induction (50—60%) was observed. It was therefore concluded that the optically active amide became coordinated to the rhodium atom—most probably *via* the oxygen atom—during the asymmetric hydrogenation reaction.

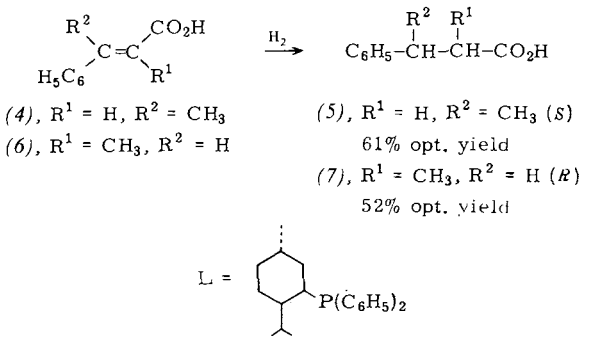
Morrison et al.[23] were the first to successfully effect asymmetric hydrogenation using a rhodium catalyst and a phosphane containing an optically active moiety[24], namely neomenthyldiphenylphosphane. The catalyst, probably a Rh^IL_3Cl complex, was prepared *in situ* from rhodium(I)-olefin complexes and neomenthyldiphenylphosphane (L); it was used to hydrogenate, *e.g.*, (*E*)-β-methylcinnamic acid *(4)* to (*S*)-3-phenylbutyric acid *(5)*, and (*E*)-α-methylcinnamic acid *(6)* to (*R*)-2-benzylpropionic acid *(7)*, in optical yields of 61 and 52% respectively (solvent: benzene/ethanol).

Dang and *Kagan*[25] synthesized the chiral bis(phosphane) *(8)* (L) from the diethyl ester of (+)-tartaric acid, and

[*] According to the authors these results are difficult to reproduce [12].

[**] Optically active phosphanes with chiral phosphorus atoms [15].

[***] Ethyl digol = $C_2H_5O-CH_2-CH_2-O-CH_2-CH_2OH$.

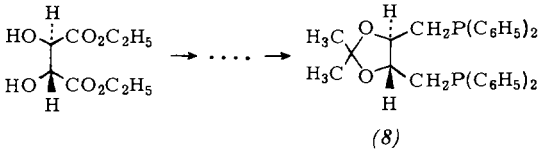


(4), $R^1 = H$, $R^2 = CH_3$
(6), $R^1 = CH_3$, $R^2 = H$

(5), $R^1 = H$, $R^2 = CH_3$ (S)
61% opt. yield
(7), $R^1 = CH_3$, $R^2 = H$ (R)
52% opt. yield

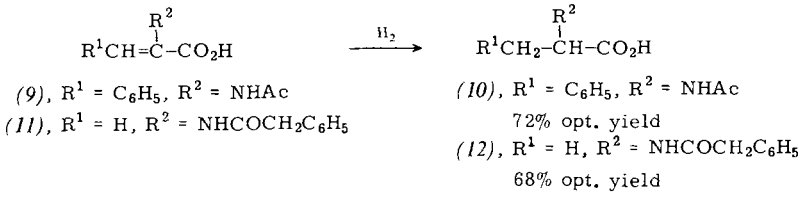
L =

used this as the chiral agent in rhodium(I)-complex-catalyzed asymmetric hydrogenation.



(8)

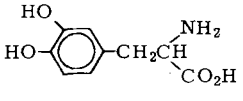
The catalyst, probably a Rh(L)ClS complex (S = solvent) generated by reaction between *(8)* and $[Rh(cyclooctene)_2Cl]_2$, assisted in effecting the reduction of α-acetylaminocinnamic acid *(9)* to (*R*)-*N*-acetylphenylalanine *(10)* and of α-phenylacetylaminoacrylic acid *(11)* to (*R*)-*N*-phenylacetylalanine *(12)*. At 20 °C and under a hydrogen pressure of one atmosphere these reactions proceeded with optical yields of 72 % and 68 % respectively (solvent: benzene/ethanol).



(9), $R^1 = C_6H_5$, $R^2 = NHAc$
(11), $R^1 = H$, $R^2 = NHCOCH_2C_6H_5$

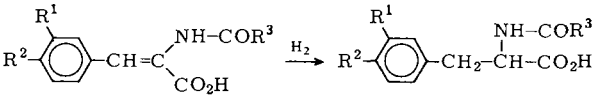
(10), $R^1 = C_6H_5$, $R^2 = NHAc$
72% opt. yield
(12), $R^1 = H$, $R^2 = NHCOCH_2C_6H_5$
68% opt. yield

The high optical yields observed using this catalyst are attributed to the conformational rigidity of the chelating bis(phosphane), and also to the part played by the acidic functional group in the substrate. In a later publication[26] by the same authors it was reported that this catalyst system effected the hydrogenation of β-substituted α-acetylaminoacrylic acid derivatives and that, *in general*, optical yields of 70—80 % were obtained. This route permits the convenient synthesis of a series of biologically important optically active amino acids including Dopa *(13)*, thereby convincingly demonstrating the potential technical and commercial importance of catalytic asymmetric hydrogenation reactions.



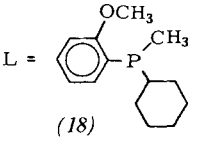
(13)

The highest optical yield yet to be achieved during catalytic asymmetric synthesis has recently been reported by *Knowles, Sabacky*, and *B. D. Vineyard*[27]. The catalysts $[RhL_2Cl]$ were prepared from rhodium(I)-olefin complexes and optically active cyclohexyl-(*o*-methoxyphenyl)methylphosphane *(18)*; hydrogenation of the α-acylaminocinnamic acids *(14)* and *(15)*, and their derivatives *(16)* and *(17)*, to the corresponding precursors of phenylalanine, *(19)* and *(20)*, and Dopa, *(21)* and *(22)*, respectively, was accomplished with product purity of 85 %—90 %. As the Horner phosphane *(18)* was probably not more than 95 % optically pure, the authors believe that this catalyst system is almost completely stereoselective in its operation.



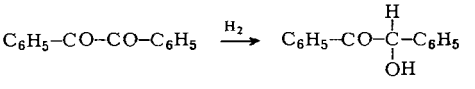
(14), $R^1 = R^2 = H$, $R^3 = CH_3$
(15), $R^1 = R^2 = H$, $R^3 = C_6H_5$
(16), $R^1 = CH_3O$, $R^2 = AcO$, $R^3 = CH_3$
(17), $R^1 = CH_3O$, $R^2 = OH$, $R^3 = C_6H_5$

(19), $R^1 = R^2 = H$, $R^3 = CH_3$
(20), $R^1 = R^2 = H$, $R^3 = C_6H_5$
(21), $R^1 = CH_3O$, $R^2 = AcO$, $R^3 = CH_3$
(22), $R^1 = CH_3O$, $R^2 = OH$, $R^3 = C_6H_5$



(18)

Ohgo, Takeuchi, and *Yoshimura*[28] have shown that high optical yields may be obtained using catalyst systems based on transition metals other than rhodium. Thus, benzil may be homogeneously hydrogenated to benzoin in an optical yield of 61.5 % using an asymmetric catalyst, bis(2,3-butanedionedioximato)cobalt(II) modified by the addition of quinine.



3. Catalytic Asymmetric Syntheses with Catalysts Comprising π-Allylnickel Halides, Phosphanes, Lewis Acids

3.1. Catalytic Asymmetric Synthesis of 3-Vinyl-1-cyclooctene and 3-Methyl-1-pentene

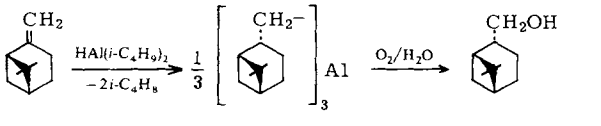
The discovery of the synthesis of 1,5,9-cyclododecatriene from butadiene at the Mülheim Institute in 1956[29] was the starting point for systematic investigations of the catalytic properties of transition metal compounds, particularly those of nickel.

Highly active catalyst systems for the dimerization, oligomerization, codimerization, and isomerization of olefins

are produced when π-allylnickel halides are activated by the addition of Lewis acids such as aluminum halides or alkylaluminum halides. An important observation, which stimulated research in this area, was made in 1963; the addition of phosphanes to the basic catalyst for the dimerization of propylene in the molar ratio 1:1 allows the course of the reaction to be controlled to produce, for instance, either 2-methylpentenes or 2,3-dimethylbutenes as the major products[30–34].

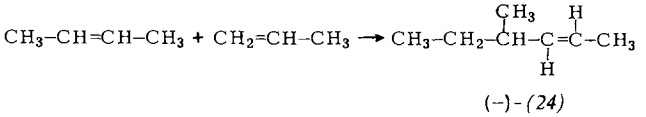
It was later found that the phosphanes were not only responsible for changes in the relative rates of formation of the respective propylene dimers, but also strongly influenced the activity of the catalyst with respect to olefin isomerization[34]. Further, in the oligomerization of ethylene the degree of oligomerization was controlled by the phosphane added, and the catalytic changes undergone by 1,5-dienes (*i.e.* the formation of five-membered ring products as opposed to the 1,3- or 1,4-diene isomerization products) were also phosphane dependent. Recent research has shown that such phosphane effects are essentially steric in nature[35].

The discovery that the course of these nickel-catalyzed reactions is extremely sensitive to the smallest change in phosphane structure soon led to the consideration that such catalysts, modified by the addition of optically active phosphanes, might possibly be employed in asymmetric synthesis. As the preparation of Horner phosphanes is generally complicated, phosphanes containing optically active organic groups which could be synthesized easily from natural products were prepared and applied for the first time in catalytic asymmetric synthesis[24]. An early success was achieved in 1967[36] when butene and propylene were found to codimerize in the presence of a catalyst consisting of π-allylnickel chloride, (−)-tris(*trans*-myrtanyl)phosphane *(23)* (prepared from β-pinene), and aluminum bromide.



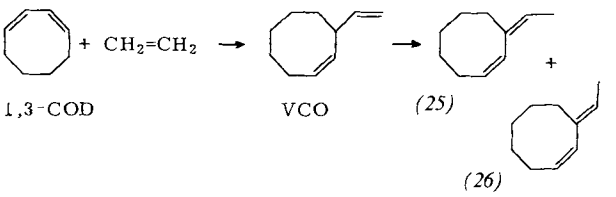
(23)

In this way it was possible to prepare small quantities of (−)-*trans*-4-methyl-2-hexene *(24)* in an optical yield of *ca.* 3%.



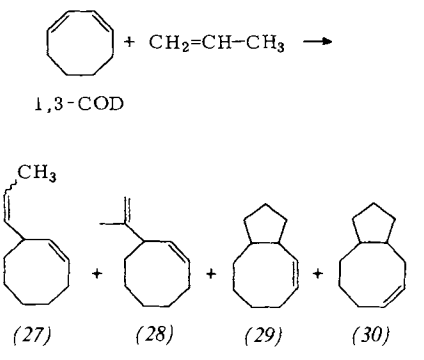
(−)-(24)

Decisive progress followed the discovery that this catalyst system facilitated smooth codimerization between cyclic 1,3-diolefins such as 1,3-cyclooctadiene (1,3-COD) and monoolefins such as ethylene or propylene[37]. Representative of the 3-substituted cycloalkenes produced is 3-vinyl-1-cyclooctene (VCO), which is formed together with the isomerization products (*Z*)- and (*E*)-3-ethylidene-1-cyclooctene [*(25)* and *(26)*] when ethylene and 1,3-COD are codimerized.



1,3-COD VCO *(25)* *(26)*

In addition, depending on the nature of the phosphane used, varying quantities of ethylene oligomers and higher molecular weight products are formed. The codimerization of propylene and 1,3-COD yields a mixture consisting principally of the four products 3-(1-propenyl)- and 3-isopropenyl-1-cyclooctene [*(27)* and *(28)*], and bicyclo[6.3.0]undec-2-ene and -3-ene [*(29)* and *(30)*].

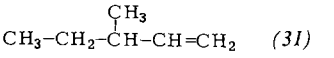


1,3-COD

(27) *(28)* *(29)* *(30)*

These codimerizations may also be controlled, by varying the phosphane employed, to yield either *(27)* or *(28)* as the main product. In these catalytic reactions chiral C atoms are produced *via* C—C bond formation, and are consequently particularly suitable for the study of asymmetric catalysis. In fact, the catalysis using optically active phosphanes does lead to the generation of the products *(25)* and *(27)*—*(30)* in optically active form; the codimerization of 1,3-COD and ethylene at 0 °C using (−)-tris(*trans*-myrtanyl)phosphane *(23)* yields VCO with a specific rotation, $[\alpha]_D^{22}$, of −19°, corresponding to an optical purity of 11—12%[38]. (Optically pure (−)-VCO (see below) has a specific rotation, $[\alpha]_D^{22.8}$, of −162.3°.)

A series of new optically active phosphanes have been prepared (Table 1) and, by varying the phosphane, the reaction temperature, and the nickel:phosphane ratio in the catalyst, it was possible to increase the optical yield of VCO from 11—12% to *ca.* 70%[39]. During the course of these experiments it was also observed that the ethylene trimer, 3-methyl-1-pentene *(31)*, produced as a side product in the codimerization of 1,3-COD with ethylene, also appeared in an optically active form. It was therefore possible to follow the dependence of the degree of asymmetric induction on the catalyst and the reaction conditions



(31)

Table 1. Dependence of the optical yield of the reaction of 1,3-COD with ethylene, to give 3-vinyl-1-cyclooctene (VCO) and 3-methyl-1-pentene *(31)*, on the nature of the phosphane employed. Catalyst: π-$C_3H_5NiCl + (C_2H_5)_3Al_2Cl_3 + PR_3$ (molar ratio: 1:2.5:1.2) in C_6H_5Cl; reaction temperature: 0°C (Standard conditions).

Phosphane	$[\alpha]_D^{22}$ [°C]	VCO		*(31)* [e]	
		direction of rotation	optical purity [%]	direction of rotation	optical purity [%]
(−)-Isopropyldimenthyl-	−158 [a]	(−)	27	(+)	17
(−)-Dimenthyl(methyl)-	−199 [a]	(−)	24	(+)	46
(−)-Tris(*trans*-myrtanyl)- *(23)*	− 12.6 [a]	(−)	12	(±)	0
(−)-*tert.*-Butyl(methyl)-*trans*-myrtanyl-	− 2.1 [b]	(−)	10	(±)	0
(+)-Dibornyl(methyl)-	+ 85.3 [a]	(+)	9.5	(−)	12
tert-Butyl(methyl)phenyl-	[c]	(−)	8.0	(−)	12.5
(−)-Menthyldimethyl-	−119 [a]	(+)	6	—	[f]
(−)-Methyl(phenyl)propyl-	[d]	(+)	5	—	[f]
(−)-Diisopropyl(menthyl)-	−102 [a]	(−)	3.5	(+)	14
(+)-Tris(2-methylbutyl)-	+110.4 [a]	(−)	3.0	(+)	27
(−)-Tris(*cis*-myrtanyl)-	− 96.2 [a]	(+)	0.5	(±)	0

[a] In benzene.
[b] Undiluted.
[c] The adduct between racemic *tert*-butyl(methyl)phenylphosphane and (+)-π-pinenylnickelbromide was recrystallized twice from ether and used as the catalyst component.
[d] As benzyl(methyl)(phenyl)propylphosphonium bromide $[\alpha]_D^{22} = -35.1°$; ($[\alpha]_D^{22} = +36.8°$ [15]).
[e] $[\alpha]_{D\,abs.}^{22} = 36.95°$ [40].
[f] No C_6 olefins were produced in the reaction.

employed by means of two, parallel, catalytic processes. Table 1 shows the dependence of the optical yield of VCO and *(31)* on the nature of the phosphane used.

The highest optical yields under these standard conditions were obtained, in the case of VCO, using (−)-isopropyldimenthylphosphane (27%) and, in the case of *(31)*, using (−)-dimenthyl(methyl)phosphane (46%). It thus appears that the menthyl group is more efficient in the optical induction than the other optically active groups studied—*cis*- and *trans*-myrtanyl, bornyl, and 2-methylbutyl. The Horner phosphane (−)-methyl(phenyl)propylphosphane gave rise to unexpectedly poor optical yields (*ca.* 5%). The values obtained for the optical purities of VCO and *(31)* show that the catalysts are to a certain extent substrate specific, since the recognizably smooth fall in the optical purity of VCO as Table 1 is descended is not reflected by a similar trend in the optical purity of *(31)*.

As the temperature is lowered the optical purity achieved generally increases. The high activity of the catalysts allows reactions to be carried out at and below −75°C (see also Section 3.2); in this way full advantage can be taken of the small differences in activation enthalpy involved when the diastereomeric catalyst-substrate intermediates react further to form the products. From the values in Table 2 a difference of 1.1 kcal/mol in the activation energy required to form the two antipodes of VCO may be calculated; this value should, however, be regarded only as an estimate of the order of magnitude of the parameter.

In the case of *(31)* the optical yield is maximized at −40°C (56%) but may be increased to 64% by reducing the reaction time from 6 h to 30 min. This result may be interpreted as showing that the initially produced enantiomer ratio is subsequently changed through temperature-dependent isomerization or oligomerization processes.

The highest optical yield of VCO yet to be observed (70%) was achieved at 0°C by employing an excess of (−)-isopropyldimenthylphosphane in the catalyst (Ni:P = 1:3.8; see Fig. 1). Thus, the excess of the phosphane has a decisive effect which may be due either to the coordination of a second molecule of the inducing phosphane to the nickel atom, or to the supression of a dissociation process. However, an increase in the P:Ni ratio causes a marked reduction in the reaction rate, and consequently even fewer moles of VCO per mole of catalyst may be obtained before the catalyst becomes inactive.

Table 2. Temperature dependence of the optical yields of (−)-(*S*)-VCO and (+)-(*S*)-*(31)*. (Reaction and catalyst as for Table 1.) Reaction time: 6 h.

Phosphane	T [°C]	VCO optical yield [%]	*(31)* optical yield [%]
(−)-Dimenthyl(methyl)-	0	24	46
	−40	42	56 (64) [a]
	−75	53 [b]	47
(−)-Tris(*cis*-myrtanyl)-	0	8	—
	−30	16	—
	−40	21	—

[a] Reaction time 30 min.
[b] Solvent CH_2Cl_2.

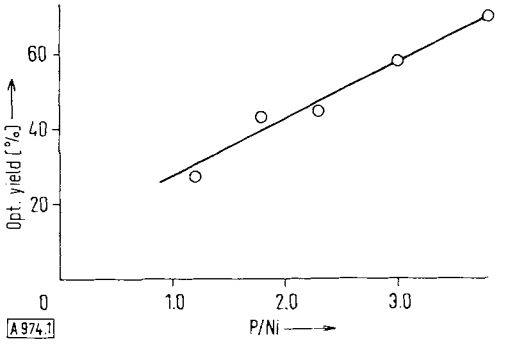
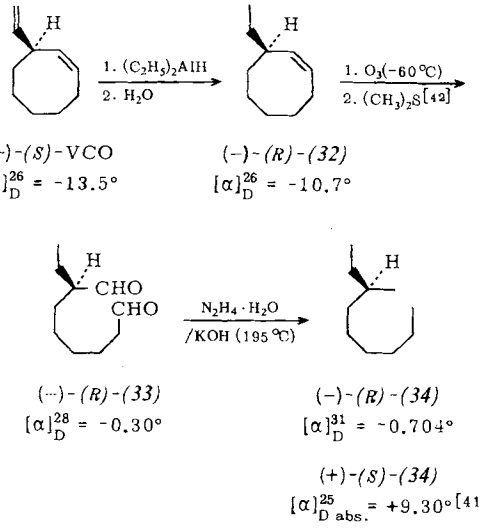


Fig. 1. Dependence of optical yield of VCO on phosphane:nickel ratio on use of (−)-isopropyldimenthylphosphane at 0°C (reaction as in Table 1).

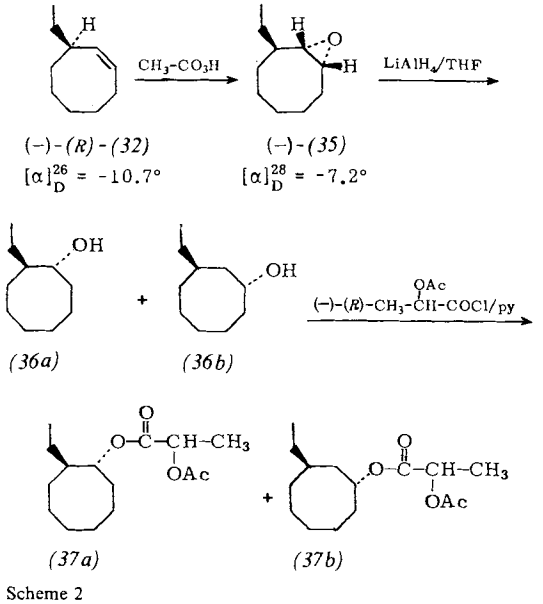
The absolute configuration and the specific rotation of optically pure (−)-VCO were determined in three independent ways[38]:

1. A sample of the catalytically prepared (−)-VCO ($[\alpha]_D^{26} = -13.5°$) was transformed into (−)-3-methylnonane *(34)* (see Scheme 1); this was then correlated with the known[41] (+)-(*S*)-3-methylnonane. In this way (−)-VCO was shown to have the *S*-configuration, and the original sample of (−)-VCO proved to be 7.6% optically pure.



Scheme 1

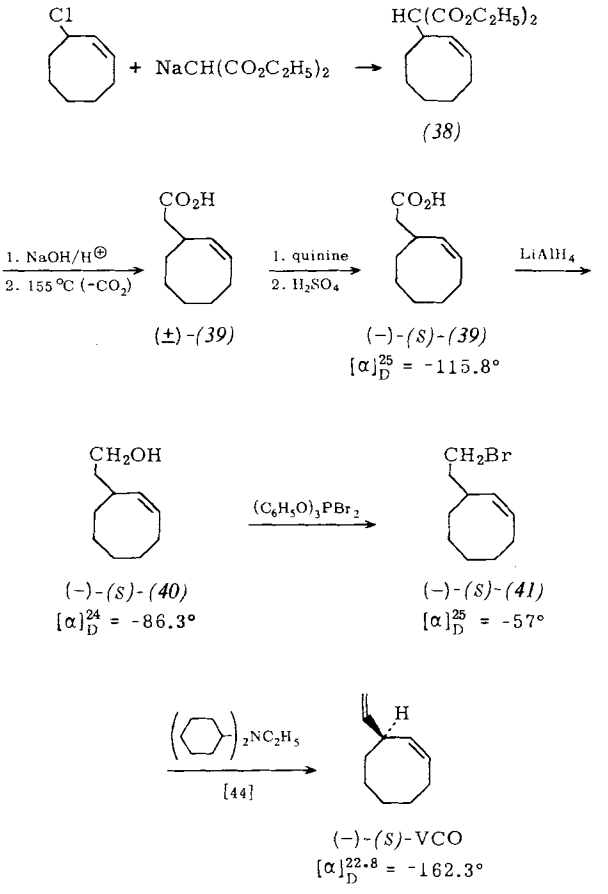
2. Epoxidation of (−)-(*R*)-3-ethyl-1-cyclooctene *(32)* with peracetic acid yielded only *trans*-3-ethyl-1,2-epoxycyclooctane *(35)*, which upon reduction with $LiAlH_4$ produced the mixture of alcohols *(36a)* and *(36b)* in the ratio 1:2.2 (see Scheme 2). This mixture of alcohols was treated with the (−)-*R* form of the acid chloride of acetylated lactic acid in pyridine, which produced a mixture of isomers *(37a)* and *(37b)*[43] giving rise to four peaks in the gas chromatogram [*R,R*- and *R,S*-forms of *(37a)* and *(37b)*]. Inspection of the ratio of *(R,R)-(37b)* to *(R,S)-(37b)*



Scheme 2

revealed that the original sample of (−)-VCO was 7.0% optically pure.

3. Optically pure (−)-(*S*)-VCO was obtained in a seven-stage synthesis *via* an intermediate racemate separation of the quinine salts of (2-cyclooctenyl)acetic acid *(39)* by fractional crystallization (Scheme 3).



Scheme 3

The synthesis shown in Scheme 3 yielded (−)-(*S*)-vinylcyclooctene with a specific rotation $[\alpha]_D^{22.8}$ of −162.3° (*c* = 4.8, C_6H_6), which corresponds to an optical purity of 8.3% for the samples of (−)-VCO $\{[\alpha]_D^{26} = -13.5°\}$ used in the above two methods. This result agrees relatively well with those of the other two methods.

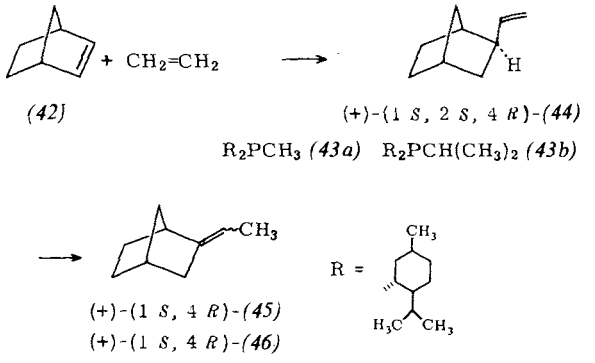
The codimerization of 1,3-COD and ethylene to give optically active 3-vinyl-1-cyclooctene is the first example of a catalytic asymmetric synthesis in which the chiral center is produced in high optical purity *via* C—C bond formation.

3.2. Catalytic Asymmetric Codimerizations of Norbornene, Norbornadiene, or (±)-2-Bornene with Ethylene[45]

The catalytic codimerizations of norbornene, norbornadiene, and (±)-2-bornene with ethylene have proved to be practically ideal examples in the study of asymmetric synthesis using the π-allylnickel halide catalysts. Since these olefins incorporate double bonds activated by ring strain, it is possible to effect the syntheses at very low temperatures.

Using a catalyst system made up of π-allylnickel chloride, triethyldialuminum trichloride, and the optically active

phosphane (−)-dimenthyl(methyl)phosphane *(43a)* or (−)-isopropyldimenthylphosphane *(43b)*, it was found that norbornene *(42)* and ethylene codimerized in chlorobenzene to give optically active *exo*-(+)-2-vinylnorbornane *(44)* as the only primary reaction product; *i.e.* the ethylene added only from the sterically less hindered side of the norbornene C=C double bond.



According to the reaction conditions and the phosphane used variable quantities of the isomerization products of *(44)*, (*Z*)- and (*E*)-2-ethylidenenorbornane *(45)* and *(46)*, are produced. In this process the chiral center at C-2 is lost but those at C-1 and C-4 remain, thereby retaining the total chirality of the molecule.

The codimerization of norbornene with ethylene under the control of (−)-isopropyldimenthylphosphane was investigated at temperatures ranging from +10 to −97 °C. Even at −83 °C the time required for all the norbornene to react was acceptable, and it was found in addition that low temperatures selectively favored the isolation of *(44)*. The most surprising result of these experiments is undoubtedly the nearly linear increase in the optical yield of (+)-*(44)* as the temperature is lowered. This relationship was practically independent of the isomerization to *(45)* and *(46)* (see Fig. 2). At −97 °C an optical yield of 80.6% was obtained, this being the highest optical yield yet observed in a catalytically asymmetric synthesis involving C—C bond formation.

minum trichloride, and a chiral phosphane yielded (+)-(1*R*, 4*S*, 5*S*)-5-vinylnorbornene *(47)* irrespective of whether the phosphane involved was *(43a)* or *(43b)*; *i.e.* in this case too the ethylene approaches the norborna-

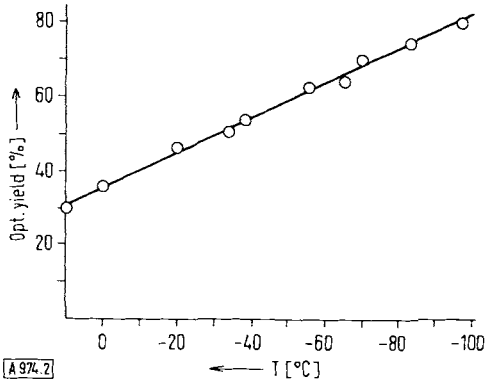


Fig. 2. Variation of the optical yield of (+)-*(44)* with temperature in the codimerization of norbornene with ethylene. Catalyst prepared from π-allylnickel chloride, $(C_2H_5)_3Al_2Cl_3$, and (−)-isopropyldimenthylphosphane *(43b)*; solvent: chlorobenzene.

diene from the *exo* side. When *(43a)* was used the optical yield of *(47)* was found to lie in the range 38—45% (see Table 3) and to be only slightly dependent on the conversion and the temperature. On the other hand, when *(43b)* was used the optical yield increased as the temperature was lowered; at −65 °C with quantitative norbornadiene conversion, *(47)* was obtained with an optical purity of 77.5%.

The reactions used in establishing the optical purity and absolute configurations of the compounds *(44)*—*(46)* and *(47)* are summarized in Scheme 4.

During the codimerization of racemic 2-bornene *(50)* with ethylene using either a (−)-*(43a)*- or a (−)-*(43b)*-modified catalyst incomplete conversion is accompanied by the preferential reaction of the (+)-2-bornene with the ethylene, leaving the substrate to become richer in (−)-2-bornene.

Table 3. Dependence of the optical yield of (+)-5-vinylnorbornene *(47)* on temperature and conversion (catalyst as in Table 1). C_9 = *(47)* + *(48)* + *(49)*; C_{11} = codimers from C_9 and ethylene.

T[°C]	t[h]	Phosphane	Norbornadiene conversion [%]	Yield [%] [a] *(47)*	Yield [%] [a] *(48)* + *(49)*	Yield [%] [a] C_{11}	C_9/C_{11}	*(47)* opt. yield [%]	mol *(47)* / mol Ni-cat.	mol C_9+C_{11} / mol Ni-cat.
−25	3	*(43a)*	60.7	34.0	2.5	24.9	1.5	45.4	36.2	65.6
−50	5.5	*(43a)*	100	46.4	3.6	15.8	3.2	38.6	81.7	115.5
−60	2.75	*(43a)*	43.7	71.0	3.9	18.0	4.2	43.2	55.5	72.5
−20	0.5	*(43b)*	30.8	23.3	12.6	18.5	2.0	62.0	12.6	29.5
−40	3	*(43b)*	100	30.7	11.3	22.4	1.9	62.8	40.4	85.6
−65	3	*(43b)*	100	49.3	13.4	11.6	5.4	77.5	86.5	130.8

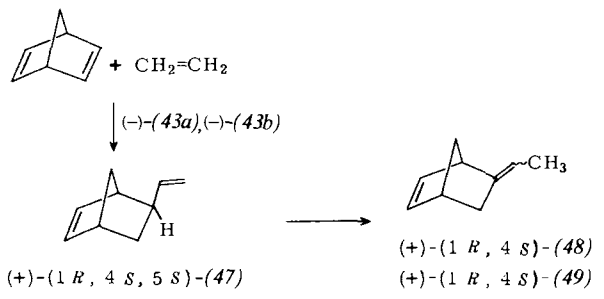
[a] Based on reacted norbornadiene; the remainder comprises higher oligomers.

From the temperature dependence of the optical yield a value of 1.5 kcal/mol was calculated for the difference in the activation energies ($\Delta\Delta E^{\neq}$) leading to the formation of (+)- and (−)-*(44)*.

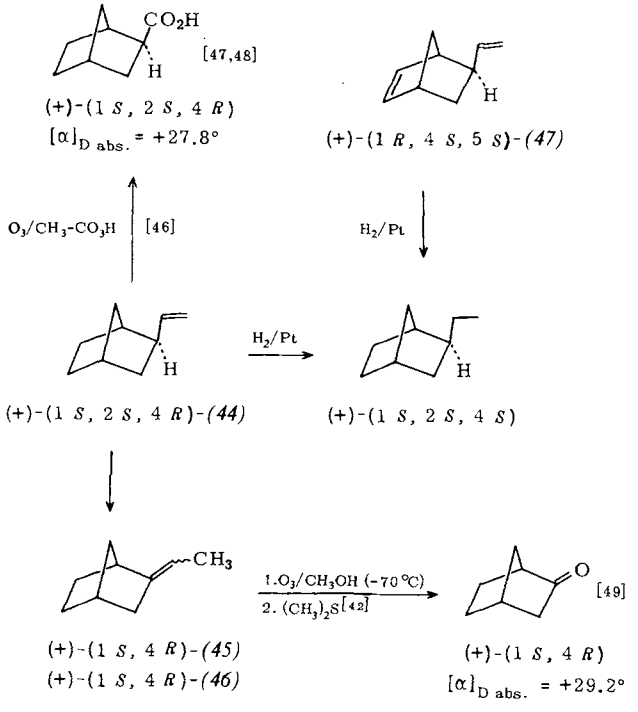
Codimerization of norbornadiene with ethylene using a catalyst made up of π-allylnickel chloride, triethyldialu-

In other words we are here concerned with an "enantioelective catalytic codimerization" reaction. It is interesting to note that in this codimerization the methyl group on C-1 of the bornene directs the reaction such that C—C bond formation takes place entirely at the 3-position of *(50)*. The reaction product was not, however, the expected

3-vinylbornane; instead its isomerization products (*Z*)- and (*E*)-3-ethylidenebornane *(51)* and *(52)* were formed. The

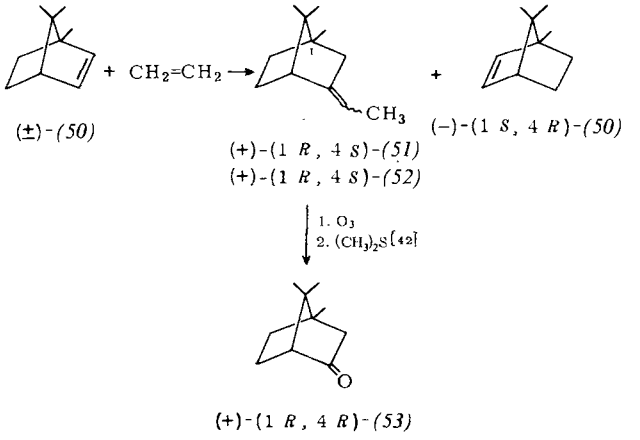


catalytically formed products *(51)* and *(52)*, showing positive rotations, possess the same configuration as (+)-2-bornene, namely the (1*R*,4*S*)-configuration.



Scheme 4. Reaction of *(44)* to *(45)*, *(46)* was catalyzed by π-$C_3H_5NiCl \cdot AlX_3 \cdot P(CH_3)_3$ [33].

The maximum optical yield of *(51)* and *(52)* to be achieved (*ca.* 20%) resulted from an experiment in which 40% of *(50)* was converted using a (−)-*(43b)*-modified catalyst at 0 °C. Ozonolysis of (+)-*(51)*, *(52)* leads to (+)-epicamphor *(53)*, and so the codimerization of (±)-*(50)* with ethylene under the influence of the optically active catalyst *(43)* (or, conversely, the codimerization of optically active 2-bornene with ethylene using an optically inactive catalyst made up of π-C_3H_5NiCl, $(C_2H_5)_3Al_2Cl_3$ and an optically inactive phosphane) opens up a new route for the preparation of optically active epicamphor.



3.3. An Attempt to Interpret Asymmetric Catalysis in Terms of a Model of the Optically Active Catalyst

The catalysts described above are generally prepared from π-allylnickel halides, Lewis acids, and phosphanes; the phosphanes are coordinatively bound to the nickel atoms, and the Lewis acid molecules interact with the halogen atoms in the π-allylnickel halide. A three-dimensional X-ray crystallographic structure of a compound of this type, *(54)*, is already available[50,51] (see Fig. 3).

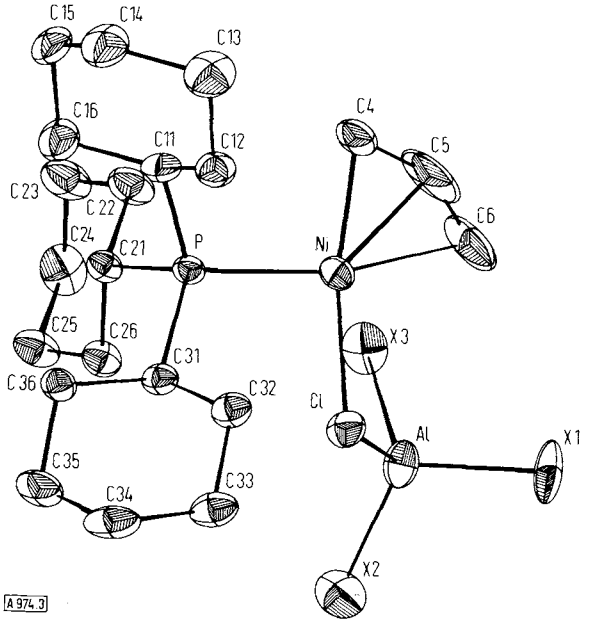
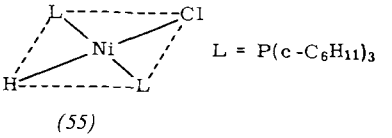


Fig. 3. Molecular structure of the complex *(54)* comprising π-allylnickel chloride, tricyclohexylphosphane, and methylaluminum dichloride.

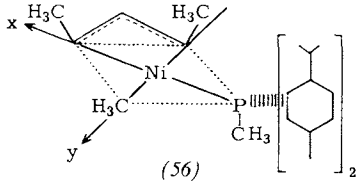
In a model experiment[34] it was shown that the π-allyl groups were lost during the first stages of the transformations undergone during olefin catalysis.

As active catalyst species a nickel hydride system is formed which could not, however, be isolated as such during the catalytic reactions, but for which known models, such as the square planar[52] L_2NiHCl complex *(55)*, exist.



(55)

In the following an attempt will be made using a model of the optically active catalyst to correlate the absolute configurations of the modifying phosphane *(43a)* and the optically active product, vinylnorbornane (VNB). The attempted correlation is based partly upon the molecular structure and the absolute configuration[53] of the complex *(56)* formed from methyl(π-1-methyl-2-butenyl)nickel and



(56)

(−)-dimenthyl(methyl)phosphane *(43a)* as determined by X-ray crystallography[54] (see Fig. 4).

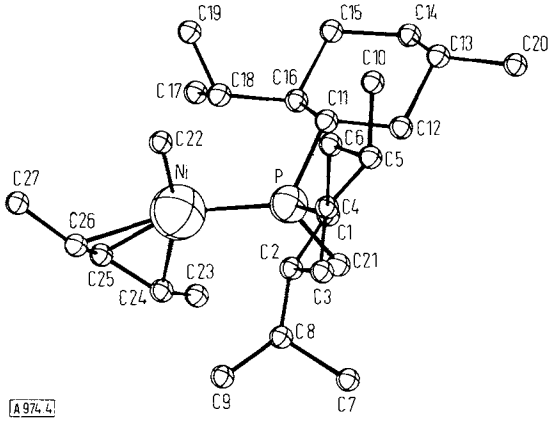


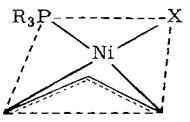
Fig. 4. Molecular structure of the complex *(56)* formed from methyl(π-1-methyl-2-butenyl)nickel and (−)-dimenthyl(methyl)phosphane *(43a)*.

The coordination about the nickel in this compound approaches square planar, the four coordination sites being occupied by the atoms C-22, C-26, C-24, and P. The two menthyl groups are oriented in a propeller-like fashion about the phosphorus atom, and their longitudinal axes are approximately perpendicular to each other.

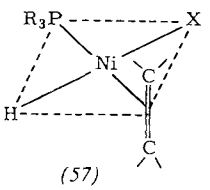
Inspection of Stuart molecular models along the direction of the x-axis reveals that the isopropyl group (C-17, C-18, C-19) of one menthyl group is situated close to the nickel atom above the *x-y* plane; the space below this plane is, however, relatively free. This observation applies, of course, to the stationary situation prevailing during a crystallographic study, and it must be remembered that in solution individual groups of atoms may move relative to others within the molecule. The static situation does, nevertheless, afford useful information as to the most favored arrangements.

The complex *(54)* has also been shown by X-ray crystallography to possess a square planar structure (see Fig. 3). This complex differs from the catalytically active *(57)* only in that in the latter two coordination sites are occupied by an olefin molecule and a hydrogen atom instead of by a π-allyl group. By analogy with the L_2NiHCl complex *(55)*, in which the phosphane ligands are *trans* to each other, the olefin in *(57)* is formulated as occupying the coordination site *trans* to the phosphane.

In the particular case of norbornene-ethylene codimerization it may also be assumed that during the catalysis the norbornene becomes bound to the nickel atom from the *exo*-side, such that no steric interaction ensues between



(54), R = c-C_6H_{11}
X = $ClAl(CH_3)Cl_2$



(57)

the methylene bridge on the olefin and the bulky complex anion X. The structural arrangement *(a)* in Figure 5 would thus seem to be the most probable representation at the start of the catalytic cycles A and B.

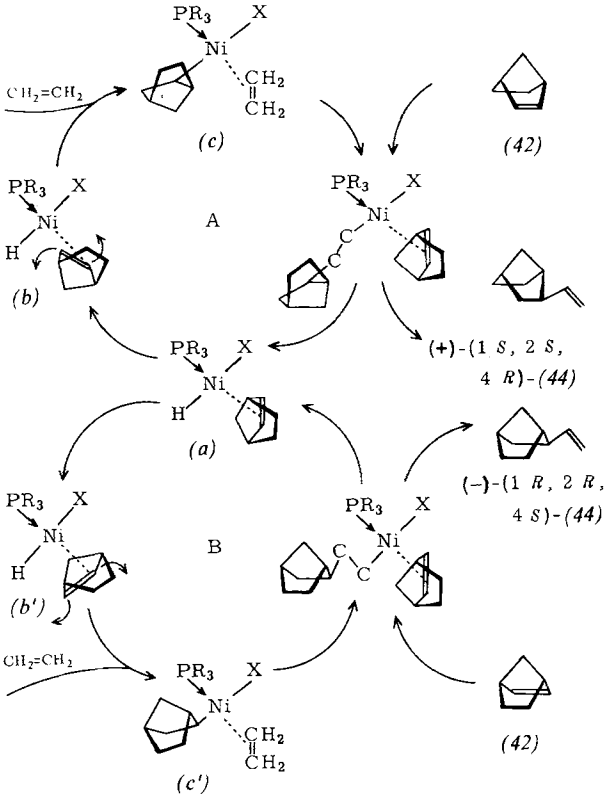


Fig. 5. Synthetic cycles leading to (+)- and (−)-vinylnorbornane *(44)*.

As the olefinic double bond lies perpendicular to the *x-y* plane of the catalyst, insertion into the Ni—H bond (during which step optical induction is already taking place) must occur either *via* a clockwise (cycle B) or an anticlockwise (cycle A) rotation of the complexed norbornene molecule. At the same time an ethylene molecule, which may act as an "accelerating ligand" in this process, can approach the *x-y* plane of the complex from above or from below. After the norbornene has inserted into the Ni—H bond the ethylene may occupy the vacated nickel coordination site.

When the above dynamic processes are simulated with a Stuart molecular model, in which the orientation of the phosphane ligand is the same as that depicted for

complex *(56)* in Figure 4, it can be seen that, whereas clockwise rotation of the norbornene molecule (cycle B) leads to an unfavorable steric interaction with a menthyl group, anticlockwise rotation (cycle A) is essentially sterically unhindered. Such a rotation leads to a norbornylnickel bond which, after ethylene insertion, yields (+)-(1*S*,2*S*,4*R*)-2-vinylnorbornane. This is the product which in fact predominates.

According to this concept, insertion of the norbornene into the Ni—H bond is accompanied by a change from a relatively unhindered steric state (where the double bond is coordinated perpendicular to the *x*-*y* plane, *trans* to the phosphane) to a state in which distinct steric interaction occurs with the phosphane causing optical induction.

4. Further Catalytic Asymmetric Syntheses and General Prospects

A review concerning the present state of research in the field of catalytic asymmetric synthesis using homogeneous transition metal catalysts would be incomplete without mention of the following additional developments. Optically active cyclopropane derivatives have been obtained with maximum optical yields of *ca.* 8%[55,56] by reacting olefins with diazo compounds in the presence of optically active copper complexes. *Yamamoto, Kumada, et al.*[57–59] have described the asymmetric hydrosilylation of olefins using Ni-, Pd-, and Pt-catalysts modified with optically active phosphanes; the highest optical yield (17.6%) was attained using the nickel complex. Recently *Pino et al.*[60,61] have effected the asymmetric hydroformylation of various aromatic and aliphatic olefins. The catalyst was the complex formed from RhCl(CO) and *(8)*[25], and optical yields ranged up to 27%.

The results so far obtained encourage us to predict that it may be possible, through the development of more refined optically active ligands, to produce catalysts which will enable homogeneous catalytic asymmetric synthesis to be as efficient as enzyme-catalyzed synthesis. At present the choice of the optically active ligand is empirical, but the accumulation of more experimental data may enable precise correlations to be made between the structure and configuration of the catalyst and the optically active reaction product. With the help of such knowledge it should be possible in the future to prepare "tailor-made" asymmetric catalysts.

The accomplishment of these goals would provide us with a means producing unlimited amounts of optically active compounds independently of natural sources, the importance of which can hardly be overstressed.

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The Allylcobalt System

By Helmut Bönnemann
Based upon the work of Helmut Bönnemann, Charles Grard, Werner Kopp, Wichard Pump, Kenjiro Tanaka, and Günther Wilke[*]

In Memory of Karl Ziegler

The following report describes the preparation and reactions of organocobalt compounds, especially the thermally unstable tris(π-allyl)cobalt and cyclooctenylcobalt compounds. The stoichiometric and catalytic transformations of these highly reactive organocobalt systems give an insight into the rôle of cobalt in homogeneous catalysis involving alkenes and alkynes.

1. Preparation of Tris(π-allyl)cobalt Systems

Tris(π-allyl)cobalt was first prepared ten years ago by *G. Wilke* and *K. Tanaka*[1] in the course of a comparative study of transition metal allyl compounds[1–3]. This thermally very unstable compound was obtained in yields of 45—50% by allyl exchange between tris(2,4-pentanedionato)cobalt(III) ($Co(acac)_3$) and allylmagnesium chloride [eq. (1)]. The reaction between cobalt(II) chloride and allylmagnesium chloride gives (in addition to a black decomposition product) tris(π-allyl)cobalt, in up to 50% yield, as a result of a disproportionation reaction [eq. (2)][3]. Although tris(π-allyl)cobalt can be prepared by both methods, the product was not obtained sufficiently pure for structural studies. Only recently has a careful reinvestigation allowed the preparation of this compound in pure form. For this reason the synthesis of tris(π-allyl)cobalt is described here in detail. This is followed by a discussion of the structural problem.

$$Co(acac)_3 + 3\,C_3H_5MgCl \xrightarrow[45\text{–}50\%]{} \underset{(1)}{(C_3H_5)_3Co} + 3(acac)MgCl \qquad (1)$$

$$2\,CoCl_2 + 4\,C_3H_5MgCl \xrightarrow[<50\%]{} \underset{(1)}{(C_3H_5)_3Co} + [C_3H_5Co^{I}] + 4\,MgCl_2 \qquad (2)$$

acac = 2,4-pentanedionate

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Bis(allyl)cobalt, which is the primary product of the reaction of cobalt(II) chloride with allyl Grignard, is not stable under normal reaction conditions (decomposing even at $-60\,^{\circ}C$) and spontaneously disproportionates into tris(allyl)cobalt *(1)* and an allylcobalt(I) species, which, in the absence of stabilizing ligands, immediately decomposes. A recently discovered artifice[5] enables half of the reactant which is lost in the disproportionation reaction to be converted into further tris(allyl)cobalt: free allyl halide and additional allylmagnesium chloride are added to the reaction mixture and, as a result, the formation of the black side-product is suppressed. The allylcobalt(I) species (resulting from the disproportionation) reacts with the allyl halide to give an intermediate bis(allyl)cobalt halide which reacts further with the allylmagnesium chloride to give the tris(allyl) compound. This combination of disproportionation and allyl halide cleavage [eq. (3)] enables a very pure product to be prepared in high yield and is also particularly useful for the synthesis of homologs containing substituted allyl groups (Table 1) which, in some cases, cannot be prepared by the route shown in eq. (1).

$$2\,CoCl_2 + 5\,C_3H_5MgCl + C_3H_5X \xrightarrow[75\%]{} \underset{(1)}{2(C_3H_5)_3Co} \quad (3)$$

$$X = \text{halide} \qquad + 4\,MgCl_2 + MgXCl$$

The success of these syntheses depends to a large extent upon the exact adherance to a number of reaction and isolation conditions[5][*]. Well resolved ^{1}H-NMR spectra cannot be obtained if the product is contaminated with traces of magnesium or halogen containing compounds. Vanishingly small amounts of decomposition products have a similar effect. The low-temperature apparatus (developed for the preparation of highly unstable metal complexes[6]) shown in Figure 1 has been found particularly useful for the preparation of tris(allyl)cobalt.

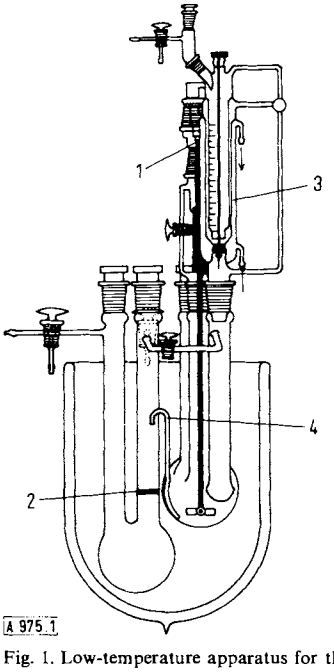


Fig. 1. Low-temperature apparatus for the syntheses of highly sensitive transition metal compounds. 1 = KPG stirrer with magnetic coupling, 2 = sintered disk (D 3), 3 = dropping funnel with cooling jacket, 4 = syphon.

[*] The cobalt salt is reacted with the Grignard reagent at -55 to $-60\,^{\circ}C$ in diethyl ether, taking care that the stationary concentration of the free Grignard reagent in solution is as low as possible. The insoluble side-products are removed by filtration at -55 to $-60\,^{\circ}C$ and the ether is evaporated. The soluble organocobalt compounds are extracted, preferably with liquid butane, to give a 0.05 M solution from which the tris(allyl)cobalt *(1)* is precipitated (as orange-red, irregular prisms) by cooling to between $-100\,^{\circ}C$ and $-130\,^{\circ}C$. For NMR purposes, the product is recrystallized several times; even in a highly pure form it must be stored at temperatures below $-70\,^{\circ}C$.

Solutions of tris(allyl)cobalt decompose at temperatures above $-50\,^{\circ}C$; if crystals are allowed to warm under argon, spontaneous deflagration occurs at $-20\,^{\circ}C$ (cf. Section 3, case 1). The compound burns with a fierce flame on exposure to air. As can be seen from Table 1, the methyl substituted derivatives are of greater stability, while the replacement of an allyl group by a cyclopentadienyl group lends unusual stability to the product. The methyl substituted compounds do not burn spontaneously in air, while the cyclopentadienyl derivative is only slowly attacked by atmospheric oxygen. The compounds shown in Table 1 are sufficiently volatile at low temperatures for their mass spectra to be studied; in each case the molecular ion corresponds to a monomer.

Table 1. Preparation and properties of some organocobalt compounds.

Complex	Dec. pt. [°C] [a]	Preparation eq.	Yield [%]	Ref.
Tris(allyl)cobalt *(1)*	−50	(1), (2), (3)	45, 50, 75	[1—5]
Tris(2-methallyl)cobalt	−30	(3)	20	[5]
Tris(1-methallyl)cobalt	−30	(3)	40	[5]
Tris(1-methylcrotyl)cobalt	−20	(1), (3)	30	[5]
Bis(allyl)(cyclopentadienyl)-cobalt *(19)*	0	[b]	78	[5]

[a] In pentane.
[b] Prepared from bis(allyl)cobalt iodide *(17a)* (see Section 3.2).

2. Spectral Properties and Structure of Tris(π-allyl)-cobalt

Because of its high sensitivity, it was some time before it proved possible to characterize tris(allyl)cobalt *(1)* on the basis of its physical data. *W. Pump* reinvestigated the problem in 1970[5] using a newly developed low-temperature technique. The following results were obtained with very pure samples.

2.1. Mass Spectrum

It proved possible to obtain interpretable spectra by using a direct injection system cooled to $-30\,^{\circ}C$. In addition to the molecular ion, elimination of C_3H_5 radicals is observed. This type of fragmentation is typical for allyl transition metal compounds.

Characteristic is the successive elimination of two H_2 molecules from the molecule ion. In addition propene is eliminated from both the molecular ion and the bis(allyl)cobalt ion ($m/e = 141$); this can be attributed to H-abstraction from an allyl group.

The spectrum also contains peaks due to ions and hydrocarbon fragments apparently formed by the coupling of the allyl groups ($124 = C_9H_{16}$, $82 = C_6H_{10}$, $67 = 82 - CH_3$);

Table 2. Characteristic masses in the spectrum of $(C_3H_5)_3Co$ *(1)*.

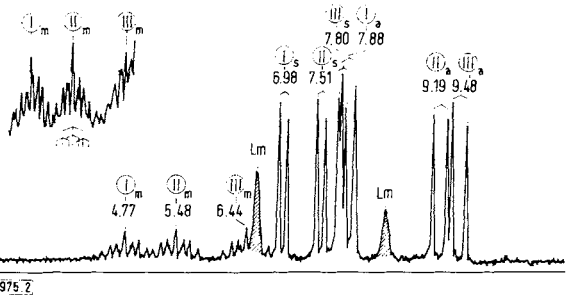
m/e	Ion	*m/e*	Ion
182	Molecule peak	101	$141-C_3H_4$
180	$M-H_2$	99	$141-C_3H_6$
178	$M-2H_2$	59	Co
141	$M-C_3H_5$	41	C_3H_5
140	$M-C_3H_6$ [a]		
138	$180-C_3H_6$ and/or $140-H_2$		

[a] A metastable ion (M = 107.7) was found for this transition.

these are the products of partial decomposition of the complex.

2.2. ^{1}H-NMR Spectrum

The ^{1}H-NMR spectrum of tris(π-allyl)cobalt shown in Figure 2 consists of three independent AM_2X_2 systems (Ⓘ Ⓘ, and Ⓘ) with intensities 1 : 1 : 1. The splitting of the *meso* protons[*] into nonets can be observed in a low-temperature CAT (computer accumulation technique) spectrum. Using decoupling procedures it proved possible to assign all the *meso*, *syn*, and *anti* signals for Ⓘ, Ⓘ, and Ⓘ.

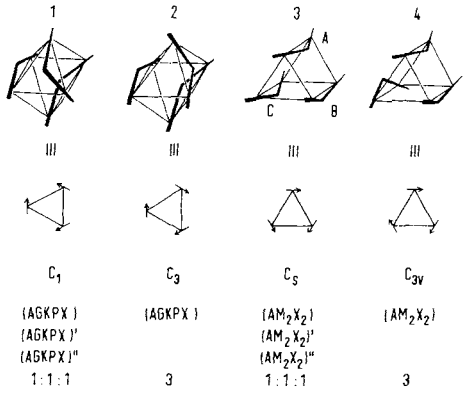


A 975.2

Fig. 2. The 60 MHz spectrum of tris(π-allyl)cobalt *(1)* at −75 °C m = *meso*, s = *syn*, a = *anti*. Ⓘ ≙ A, Ⓘ, Ⓘ ≙ B, C (see formula 3 in Fig. 3).

It is possible to arrange the three allyl groups around the central atom in four different ways: two trigonal prismatic and two octahedral (Fig. 3). Of these possibilities only the prismatic structure 3 is in agreement with the observed spectrum since only this form can generate three independent AM_2X_2 spin systems[**].

Accordingly, the allyl groups in tris(π-allyl)cobalt *(1)* adopt two different arrangements: two almost parallel basal groups (B and C) and an axial group A. This characteristic structural feature appears to be reflected in the chemical



A 975.3

Fig. 3. Possible arrangements of the allyl groups in tris(π-allyl)cobalt *(1)*.

properties of tris(π-allyl)cobalt since the basal and axial allyl groups are of differing reactivity.

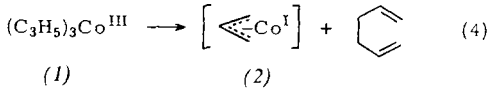
The ^{1}H-NMR spectrum of tris(1-methylcrotyl)cobalt can be interpreted as evidence that the substituted compounds also have a prismatic structure similar to tris(π-allyl)cobalt *(1)*. The interpretation of the ^{1}H-NMR spectra of the unsymmetrically substituted tris(allyl)cobalt compounds, *e.g.* tris(π-crotyl)cobalt, is greatly complicated by the presence of stereoisomers. This problem has been discussed elsewhere for the case of bis(π-crotyl)nickel[2a].

3. Reactions of Tris(π-allyl)cobalt

The allyl groups in *(1)* are of differing reactivity and three types of reaction can be distinguished.

1. Reactions involving the loss of all three allyl groups: The allyl groups in tris(π-allyl)cobalt are cleaved at −40 °C in an atmosphere of hydrogen to give propane. When recrystallized tris(π-allyl)cobalt is cautiously warmed to between −40 and −30 °C, 80% of the allyl groups are to be found in the organic decomposition product as C_1 to C_9 hydrocarbons. These compounds are the product of C—C coupling ($\Sigma \approx 1.7$ allyl groups), H-transfer ($\Sigma \approx 0.8$ allyl groups) and C—C bond cleavage ($\Sigma \approx 0.1$ allyl groups). Thus approximately two allyl groups react by coupling—a reaction commonly observed in allyl-transition metal compounds—while the hydrogen transfer and C—C cleavage reaction seem to be characteristic for cobalt. The facile hydrogen migration reaction is also observed in the catalytic reactions (see Section 6).

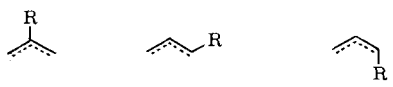
2. Reductive elimination of the basal allyl groups B and C from *(1)* with liberation of a coordinatively unsaturated allylcobalt(I) species *(2)*. It is possible to trap *(2)* by complexation with neutral ligands or by oxidative addition reactions (cf. Sections 3.1 and 3.2).



(1) *(2)* (4)

Reactions of this type are characterized by a change in the formal oxidation number of the cobalt from (III) to (I).

[*] The nomenclature for the position of a substituent in the π-allyl group is as follows:



meso *syn* *anti*

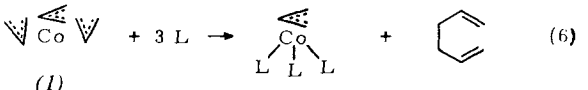
[**] On the basis of ^{1}H-NMR data, a similar prismatic structure has been assigned by *J. K. Becconsall* and *S. O'Brien* [7] to the thermally stable tris(π-allyl)rhodium. An X-ray structural analysis of the rhodium compound carried out by *C. Krüger* in our Institute showed at least that the arrangement of the allyl groups A, B and C correspond to formula 3 in Fig. 3, although a refinement was not possible because of decomposition of the sample in the X-ray beam.

3. Nucleophilic attack and replacement of the axial allyl group in *(1)* by an anion X (see Section 3.2), *e.g.* eq. 5:

$$\underset{(1)}{(C_3H_5)_3Co} + HX \longrightarrow (C_3H_5)_2CoX + C_3H_6 \qquad (5)$$

3.1. The Action of Neutral Ligands

Ligand molecules having free electron pairs cause coupling of the basal allyl groups in tris(π-allyl)cobalt systems such as *(1)* to give 1,5-hexadiene, which is displaced from the metal. This process can be followed by ^{1}H-NMR spectroscopy: when a solution of tris(π-allyl)cobalt is treated with diolefins the signals assigned to the basal allyl groups ⓘⓘ and ⓘⓘⓘ (see Fig. 2) disappear slowly above −35 °C, while the spin system Ⓘ assigned to the axial allyl group remains unchanged. The allylcobalt(I) species *(2)* can be trapped in the form of the stable complex *(3)*[8,9] by using CO or PF_3 as the ligand.

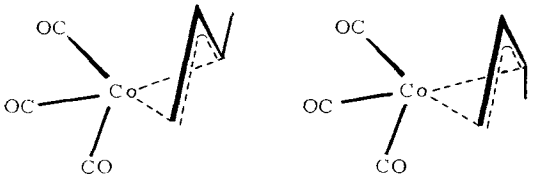


(6)

(1)

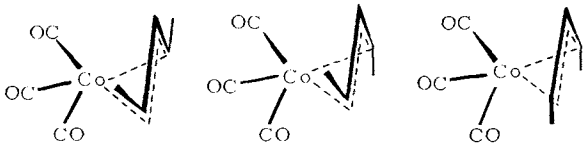
(3a), L = CO
(3b), L = PF_3

Analogous tricarbonyl complexes can be prepared at low temperatures from tris(π-crotyl)cobalt or the 1,3-dimethylallyl derivative; it has been possible, by means of ^{1}H-NMR spectroscopy, to determine quantitatively the *syn-anti* ratio in what was originally the axial allyl group. In the case of the π-crotylcobalt derivatives *(4)* and *(5)* the "axial" allyl group exists to 80% in the thermodynamically preferred *syn* form.



syn, *(4)* *anti*, *(5)*

The "axial" allyl group in tricarbonyl(1-methylcrotyl)cobalt could adopt the *syn/anti* conformations *(6)*, *(7)* and *(8)*; at −20 °C[*] only *(6)* and *(7)* are present in the ratio 4:1[**].



syn/syn *syn/anti* *anti/anti*

(6) *(7)* *(8)*

[*] A *syn/anti* transition at this temperature was ruled out.

[**] The tricarbonyl complexes *(4)*—*(7)* have been prepared earlier by other methods; the *syn/anti* ratio varies according to the method of preparation[10–12].

In this context it is of interest that the presence of different substituents on the terminal atoms of the allyl group creates a chiral tris(π-allyl)cobalt system (Fig. 4).

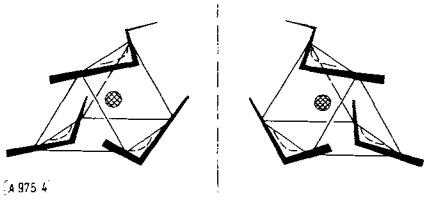
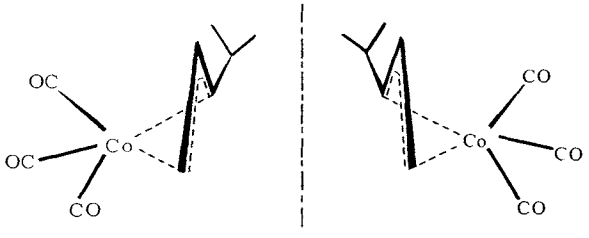


Fig. 4. The chirality of tris(π-allyl)cobalt.

We have prepared an analogous chiral π-crotylcobalt system *(9)* from $NaCo(CO)_4$ and 1-chloro-4-methyl-2-pentene, using published procedures[8]:



(9a) *(9b)*

It can be seen from the ^{1}H-NMR spectrum of the complex (Fig. 5) that *(9)* exists only as the *syn* isomer. The diastereotopic splitting of the signals ⑥ and ⑦ assigned to the methyl protons in the prochiral π-4-methyl-2-pentenyl group bonded to cobalt clearly establishes the chirality of compound *(9)*.

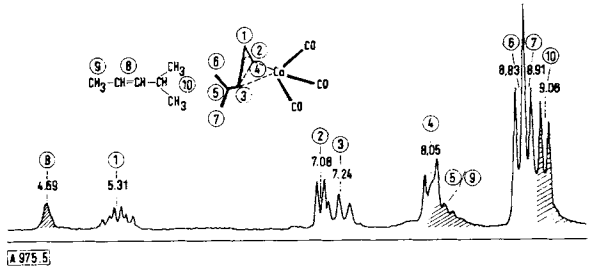
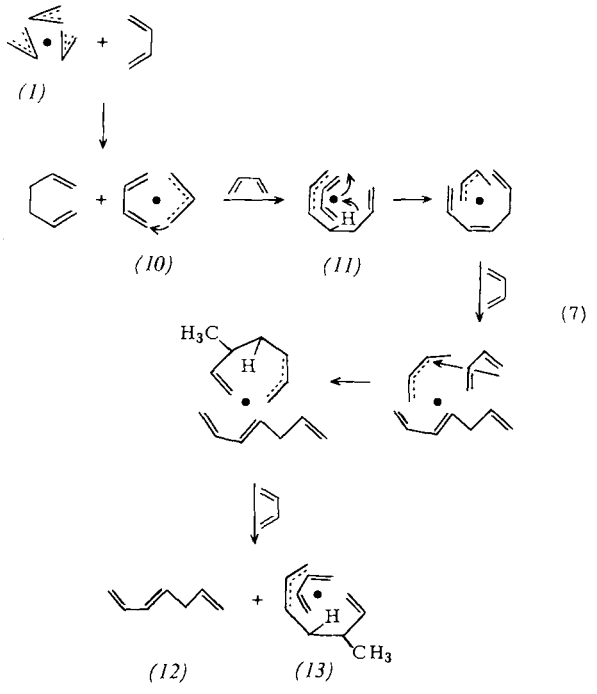


Fig. 5. The ^{1}H-NMR spectrum of tricarbonyl(π-4-methyl-2-pentenyl)cobalt (measured at −80 °C without solvent and using a Varian XL-100).

3.1.1. The Stoichiometric Reaction of Tris(π-allyl)cobalt with Butadiene[13,14]

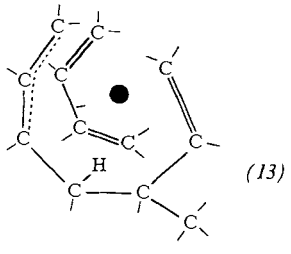
The difference in reactivity between the basal and axial allyl groups in tris(π-allyl)cobalt can be followed in a stepwise manner by allowing the complex to react with stoichiometric amounts of butadiene. The initial reaction at −40 °C is the reductive elimination of the basal groups to give the intermediate complex *(10)* (the point represents the cobalt atom) which can be observed in the ^{1}H-NMR spectrum[5]. At −15 °C insertion of a second molecule of butadiene into the Co—C bond of the allyl group occurs to give a butadiene(heptadienyl)cobalt intermediate *(11)* which can be identified mass spectroscopically (*m/e* = 208). This is followed by elimination of a β-hydrogen atom and its transfer to a further butadiene molecule. Release of a stoichiometric amount of heptatriene *(12)* leads to

the formation of the stable complex *(13)* which was first prepared by *Natta, Pino et al.*[15] by another route.



(7)

It can thus be seen that *(13)* is the key intermediate in the dimerization of butadiene initiated by tris(π-allyl)cobalt (cf. Section 6.1), a fact which had been suggested as early as 1966[2b]. The steric arrangement of the organic groups around the cobalt is based upon an X-ray structural analysis[16].



(13)

Two butadiene molecules are coupled together to form a chain (branched in the 5-position) which is bonded to the cobalt atom by means of a π-allyl group and a vinyl double bond. A third butadiene molecule is coordinated to the cobalt in a single-*cis* conformation.

3.1.2. Bimetallic Complexes

The allylcobalt(I) species *(2)* can also be stabilized, by means of organometallic ligands, in the form of a bimetallic complex[5]. With bis(allyl)magnesium a yellow-ocher compound *(14)* is produced, which is stable at room temperature.

$$\underset{(1)}{(C_3H_5)_3Co} + \underset{}{(C_3H_5)_2Mg} \xrightarrow[-40\,^\circ C]{} \underset{(14)}{C_3H_5CoMg(C_3H_5)_2} + 1,5\text{-hexadiene} \qquad (8)$$

The reaction with allyllithium under the same conditions produces a 1:2-adduct *(15)*.

$$\underset{(1)}{(C_3H_5)_3Co} + 2C_3H_5Li \longrightarrow \underset{(15)}{C_3H_5Co(LiC_3H_5)_2} + 1,5\text{-hexadiene} \qquad (9)$$

Both *(14)* and *(15)* are generated in completely insoluble forms. The allylcobalt moiety in *(14)* can be cleaved with iodine and trapped as allylcobalt diiodide (cf. Section 3.2).

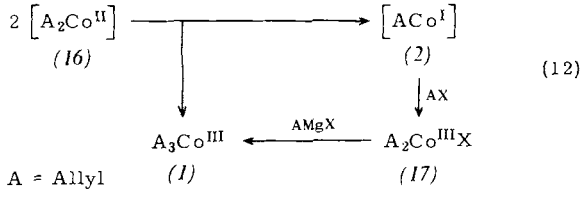
$$(14) + 2I_2 \longrightarrow C_3H_5CoI_2 + MgI_2 + 1,5\text{-hexadiene} \qquad (10)$$

3.2. Allylcobalt Halides

Allylnickel halides can be prepared by a cleavage reaction involving nickel(0) complexes and allyl halides [eq. (11)][2c] (COD = 1,5-cyclooctadiene).

$$(COD)_2Ni + CH_2{=}CH{-}CH_2X \longrightarrow \tfrac{1}{2}\left[\text{allyl-Ni-X}\right]_2 + 2\ COD \qquad (11)$$

The new variation of the synthesis of tris(allyl)cobalt shown in eq. (3) already contains an indication that cleavage of the allyl halide (similar to that shown in eq. (11)) can occur with the allylcobalt(I) intermediate *(2)*.

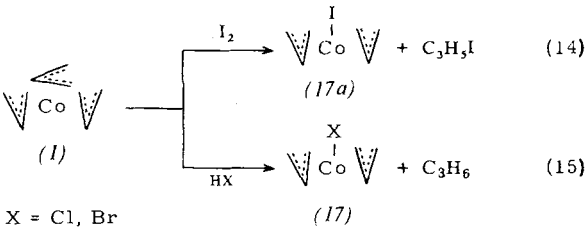


(12)

The Co^I intermediate *(2)*, formed by disproportionation of the unstable complex *(16)*, cleaves the allyl halide AX [eq. (12)] and releases an intermediate bis(allyl)cobalt halide *(17)*. This oxidative addition reaction[5] can be used to convert tris(π-allyl)cobalt *(1)* quantitatively into bis(allyl)cobalt iodide *(17a)* [eq. (13)].

$$\underset{(1)}{A_3Co} \xrightarrow[-50\,^\circ C]{COD} \underset{(2)}{[ACo^I]} \xrightarrow{AI} A_2CoI \qquad (13)$$

On the other hand it is possible to exchange the axial allyl group of *(1)* for halogen by means of a nucleophilic

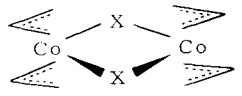


(14)

(15)

substitution reaction with elemental iodine or hydrogen halide at −55 °C, eqs. (14) and (15) [cf. eq. (5)].

The bis(allyl)cobalt halides *(17)* are produced in the reactions (13), (14) and (15) as beautiful red crystals. They are thermally sensitive, extremely insoluble, and probably exist as dimers [eq. (17)] in which the bridging halogen atoms function as double axial groups



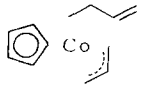
(18)

X = Cl, Br, I

Exchange of the halogen in *(17)* allows the introduction of other groups into the bis(allyl)cobalt system. For example, one can prepare bis(allyl)cyclopentadienylcobalt *(19)* from bis(allyl)cobalt iodide *(17a)*[5].

$$(C_3H_5)_2CoI + C_5H_5Li \longrightarrow \underset{(19)}{C_5H_5Co(C_3H_5)_2} \qquad (16)$$
$$\underset{(17a)}{}$$

The ^{1}H-NMR spectrum of *(19)* indicates that one of the allyl groups has adopted a σ-form, thereby avoiding the introduction of more than 18 electrons into the outer electronic shell of cobalt.



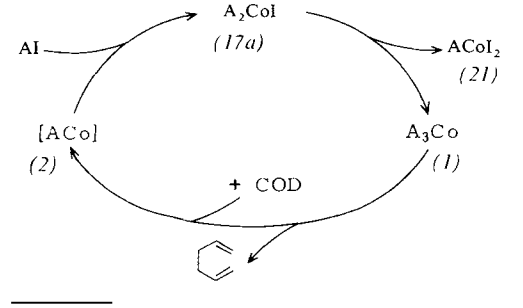
(19)

In this case also the addition of olefins causes the displacement of the allyl groups from cobalt and cyclopentadienyl-(diene)cobalt complexes *(20)* result[*].

$$(Cp)Co(C_3H_5)_2 + \text{diene} \longrightarrow \underset{(20)}{(Cp)Co(\text{diene})} + \text{1,5-hexadiene} \qquad (17)$$

Cp = π-cyclopentadienyl
diene = for example, butadiene, 1,5-cyclooctadiene, *cis*-1,2-divinylcyclobutane

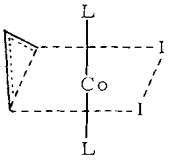
At temperatures above −45 °C, bis(allyl)cobalt iodide *(17a)* undergoes a ligand exchange reaction in which, in addition to tris(allyl)cobalt, a stable allylcobalt diiodide *(21)* is formed. Under similar conditions a mixture of *(1)* and allyl iodide in the presence of 1,5-cyclooctadiene undergoes a series of cleavage and ligand exchange reactions to give *(21)* in quantitative yield[5].



(18)

[*] This class of compounds has already been prepared by other methods [17—20].

Allylcobalt diiodide *(21)* forms green crystals which melt at +10 °C without decomposition. In the presence of additional ligands, *e.g.* phosphanes or pyridine, 2:1 adducts are quantitatively formed; presumably these have an octahedral structure, *e.g. (22)* (L = PR_3, pyridine).



(22)

4. Preparation of the 1,5-Cyclooctadiene(cyclooctenyl)cobalt System

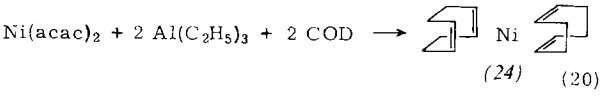
4.1. Reduction with Organoaluminum Compounds

In 1960 *Wilke et al.*[21a] discovered a general synthetic method for the preparation of low-valent transition metal complexes:

$$M'X_n + nM-R \xrightarrow[-nMX]{} \underset{(23)}{M'R_n} \xrightarrow{mL} L_mM' + nR \qquad (19)$$

M' = transition metal, M = main group metal, R = alkyl, L = ligand

From the reaction of bis(pentanedionato)nickel and triethylaluminum with COD as ligand one obtains Ni(COD)$_2$ *(24)*, *i.e.* the alkyl intermediate *(23)* decomposes with resulting reduction of the metal to the zero-valent state[21b].



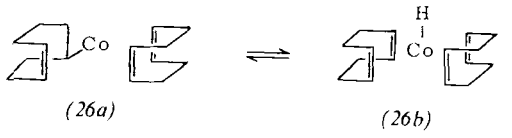
(20)

In 1966 *Grard*[22,23] extended this reaction to cobalt. The reaction of tris(pentanedionato)cobalt(III) with alkyl aluminum in the presence of COD occurred smoothly to give a diamagnetic cobalt(I) complex having the composition *(25)*. In other words, in the case of cobalt the reduction of the alkyl intermediate *(23)* does not proceed beyond the monovalent stage.

$$Co(acac)_3 + 3AlR_3 + 2COD \rightarrow \underset{(25)}{(COD)_2Co{-}R} + 3AlR_2(acac) + 2[R^\bullet] \qquad (21)$$

R = C_2H_5, *n*-C_3H_7, *n*-C_4H_9, *i*-C_4H_9, *n*-C_8H_{17}

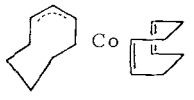
It is possible to generate the parent compound *(26)* in this series by using dialkylaluminum hydride as reducing agent. Complex *(26)* forms black, lustrous crystals which ignite spontaneously in air. Although the 1,5-cyclooctadiene(σ-cyclooctenyl)cobalt complex *(26a)* is in equilibrium with the bis(1,5-cyclooctadiene)cobalt hydride *(26b)* [cf. eqs. (28) and (30)] in solution, it is possible that one of these two forms is present in the crystalline compound. An X-ray structural analysis would clarify this point.



(22)

(26a) (26b)

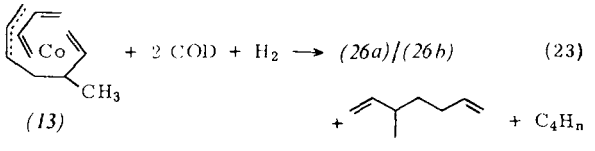
Use of an excess of dialkylaluminum hydride leads to the by-product 1,5-cyclooctadiene(π-cyclooctenyl)cobalt which results from an unrelated reaction (cf. Section 5):



(26c)

4.2. Displacement by Hydrogenation[26]

A second synthetic route to *(26a)* and *(26b)* involves the cobalt(I) species butadiene(methylheptadienyl)cobalt *(13)*. The open-chain enyl group is cleaved by hydrogen and, in the presence of COD, *(26a)* and *(26b)* are formed quantitatively.



(23)

(13)

4.3. Reduction with Sodium[24]

In 1968 *Otsuka* and *Rossi*, inspired by the initial reports[23] of *Grard*'s work, began studying the system *(26)*. On reducing $CoCl_2$ in pyridine/THF with sodium in the presence of COD they obtained 1,5-cyclooctadiene(π-cyclooctenyl)-cobalt *(26c)* in the form of dark brown leaflets.

$$CoCl_2 + 2COD + 2Na \xrightarrow[25\%]{} \underset{(26c)}{\pi\text{-}C_8H_{13}CoC_8H_{12}} \quad (24)$$

Deuteration experiments have shown that the hydrogen atom, needed to produce *(26c)*, does not originate from the pyridine.

4.4. Electrochemical Reduction[25]

Lehmkuhl et al. have developed an electrochemical synthesis for 1,5-cyclooctadiene(π-cyclooctenyl)cobalt *(26c)* [eq. (25)]. In this case methanol or ethanol functions as the proton donor.

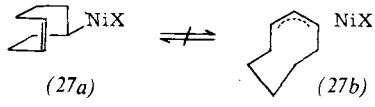
$$Co(acac)_2 + 2COD + H^{\oplus} \xrightarrow{+e^{\ominus}(cath.)} \underset{(26c)}{\pi\text{-}C_8H_{13}CoC_8H_{12}} \quad (25)$$

5. Structural Consideration and Reactions of 1,5-Cyclooctadiene(cyclooctenyl)cobalt Systems

Differing physical properties indicate that the product from the organoaluminum synthesis and the hydrogenation reaction is not identical with that produced by alkali metal or electrochemical reduction (cf. Section 4.1 to 4.4). *Otsuka* and *Rossi*[24] have shown that *(26c)*[*] is not in equilibrium with the other isomers while our experiments[26] show that *(26a)* and *(26b)* are in equilibrium with each other in solution but not with *(26c)*.

$$(26a) \rightleftharpoons (26b) \not\rightleftharpoons (26c) \quad (26)$$

These findings are consistent with those for the analogous cyclooctenylnickel compounds[28–33]: the σ-enyl and π-allyl forms *(27a)* and *(27b)* are stable and are not interconvertible.



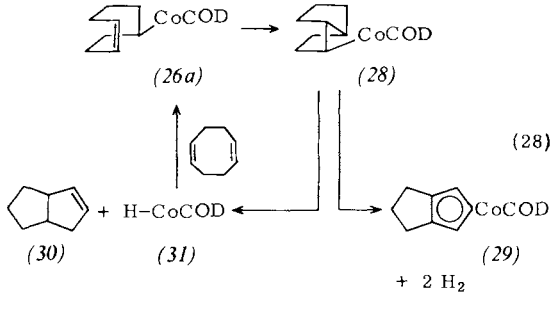
(27)

(27a) (27b)

X = acac[28,29], Br[30,31], CH_3[32,33]

As expected *(26a)* and *(26b)* are more reactive than 1,5-cyclooctadiene(π-cyclooctenyl)cobalt *(26c)*; the former are spontaneously inflammable and decompose at 40 °C, while the latter is only slowly attacked by atmospheric oxygen and melts at 65 °C.

Solutions of *(26a)* and *(26b)* are slowly converted at +40 °C into the cyclopentadienylcobalt derivative *(29)*. Apparently, under these conditions the σ-cyclooctenyl group undergoes transannular ring contraction to give the perhydropentalenyl group *(28)* from which hydrogen is eliminated to give stable *(29)*. β-H elimination to give *(30)* is observed to a lesser extent. The presence of free 1,5-cyclooctadiene results in addition to *(31)* with regeneration of *(26a)*. This process, by which COD is catalytically isomerized to *(30)*, continues until the active catalytic species *(31)* is completely converted into the catalytically inactive complex *(29)*.



(28)

(26a) (28) (30) (31) (29)

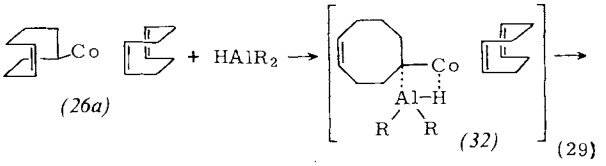
+ $2H_2$

Reaction with diisobutylaluminum hydride causes quantitative cleavage of the σ-enyl group and its elimination as cyclooctene. Presumably the reaction occurs as shown in eq. (29) with the initial displacement of the coordinated double bond of the σ-cyclooctenyl group from the cobalt and generation of a bridged cobalt-aluminum species *(32)*[**]. The intermediate *(32)* can react further by transfer-

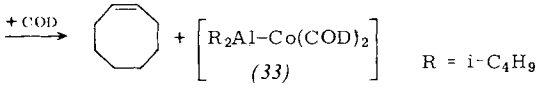
[*] The arrangement of the organic groups around the Co atom in *(26c)* has been established by X-ray structural analysis [27].

[**] For a comparison with the corresponding results obtained in the aluminum-nickel system, see the accompanying article: *K. Fischer, K. Jonas, P. Misbach, R. Stabba,* and *G. Wilke,* Angew. Chem. *85*, 1002 (1973); Angew. Chem. internat. Edit. *12*, 943 (1973).

ring the bridging hydrogen atoms to the enyl group, a step which should be accompanied by formation of the bimetallic complex *(33)*.

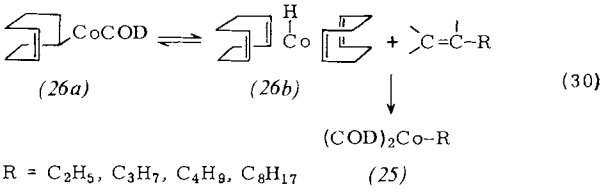


(29)



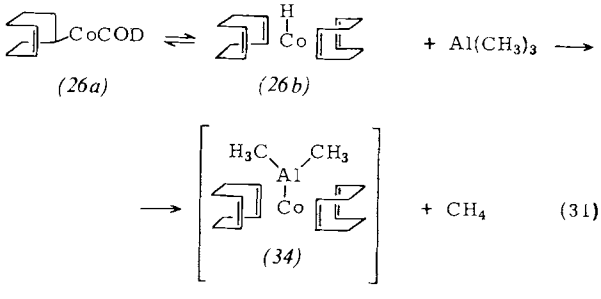
Interestingly, excess 1,5-COD is isomerized to 1,3-COD. This observation is of relevance to the discovery that the use of excess dialkylaluminum hydride in the synthesis of *(26)* is accompanied by the formation of the π-allyl form *(26c)*, which may be derived from 1,3-COD.

The σ-cyclooctenyl compound *(26a)* reacts with monoolefins through the hydride form *(26b)* (with which it is in equilibrium): addition occurs to give an alkyl bis(cyclooctadiene)cobalt *(25)*.



(30)

The hydrogen atom of the hydride form *(26b)* reacts quantitatively with trimethylaluminum with liberation of methane: a red brown diamagnetic complex is deposited from the solution at 0 °C which, although it has not been further characterized, presumably has structure *(34)*. Formally *(34)* can be compared with $NaCo(CO)_4$.

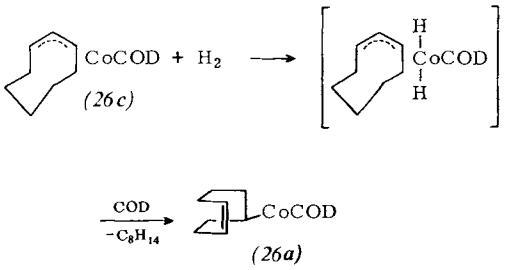


(31)

We have already mentioned that the π-form *(26c)* is less reactive than the σ-enyl isomer *(26a)* and does not react with either monoolefins or trimethylaluminum[*]. Displacement of the π-cyclooctenyl group as cyclooctene can, however, be effected by hydrogenation and in this way it is possible to convert the π-allyl form into the σ-derivative *(26a)* [eq. (32)].

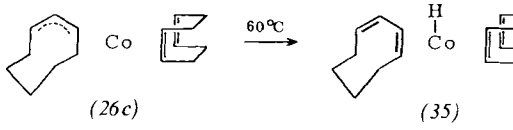
The rearrangement shown in eq. (33) indicates, however, that at higher temperatures the π-cyclooctenyl compound *(26c)* can react through an additional hydride form *(35)*.

[*] The ^{1}H-NMR spectrum of a 1:1 mixture of $Al(CH_3)_3$ and *(26c)* is identical with a superimposition of the spectra of the pure components.

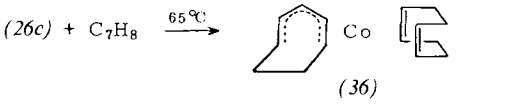


(32)

It is in this sense that *(26c)* reacts with excess cycloheptatriene: a π-cycloheptadienylcobalt complex *(36)*[34] is produced, presumably by addition of *(35)* to the seven-membered ring.

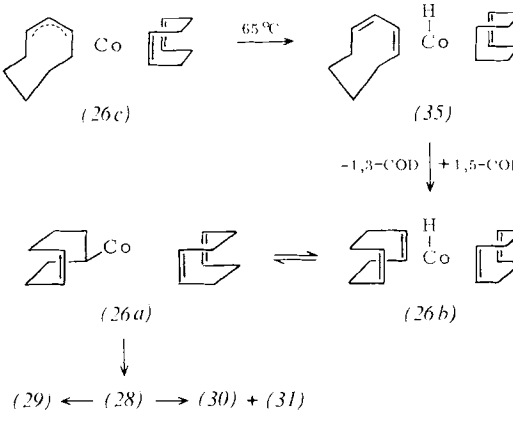


(33)



(34)

The formation of *(29)* and *(30)* from the reaction of *(26c)* with COD at temperatures above +60 °C has been reported on several occasions[25,35] and can also be regarded as proceeding *via* the hydride form *(35)* [eq. (35)]. Under the reaction conditions the compounds *(26c)*, *(35)*, *(26b)* and *(26a)* are not isolable.

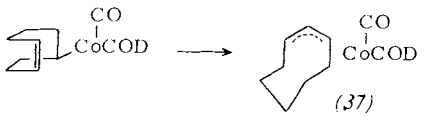


(35)

In the first step the 1,3-cyclooctadiene is displaced by the better chelating ligand 1,5-COD to give the hydride *(26b)*, which reacts further in the σ-enyl form *(26a)* according to eq. (28).

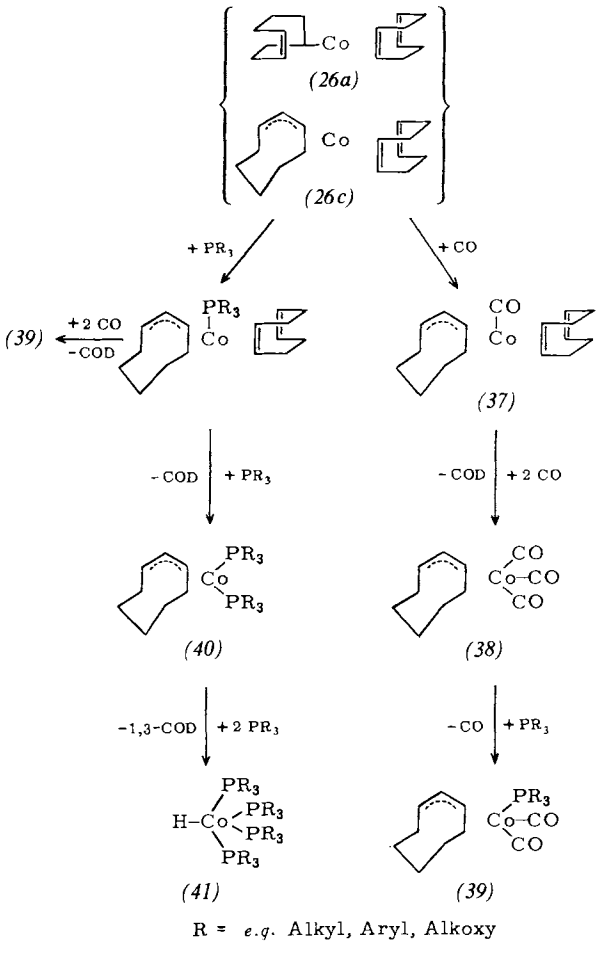
5.1. Reaction with Neutral Ligands

In the cyclooctenyl compounds *(26)* the coordination number of the cobalt atom does not exceed 4. Hence the compounds absorb carbon monoxide at low temperature[22,26,36]; interestingly, the same π-cyclooctenyl derivative *(37)* is formed both from *(26a)* and from *(26c)*. This would indicate, therefore, that the complexation of



(36)

an additional ligand causes isomerization of the σ-enyl group into a π-allyl form.



R = *e.g.* Alkyl, Aryl, Alkoxy

Additional CO displaces the 1,5-cyclooctadiene from *(37)* and produces the tricarbonylcobalt complex *(38)*[22,33,36]. *(38)* is related to the π-allyl(tricarbonyl)cobalt complex *(3a)*. PF_3 reacts with *(26)* to give the corresponding tris(ligand) complex[37]. One of the carbonyl groups bonded to the cobalt can be selectively substituted by reaction with phosphanes of type PR_3 to give the compounds *(39)*[22,26]. If *(26)* is reacted directly with phosphanes then, in general, the bis(ligand) adduct *(40)* is produced[33,38]. Although the π-allyl group in π-allyl(tricarbonyl)cobalt *(3)* cannot be displaced by reaction with CO[3], excess of phosphane reacts with *(26)* to produce compounds of the type *(41)*. A detailed study[38] of the effect of ligands has shown that equilibration occurs: the position of equilibrium depending upon the π-acceptor and σ-donor properties of the complex partner.

6. Processes Catalyzed by π-Allylcobalt Complexes

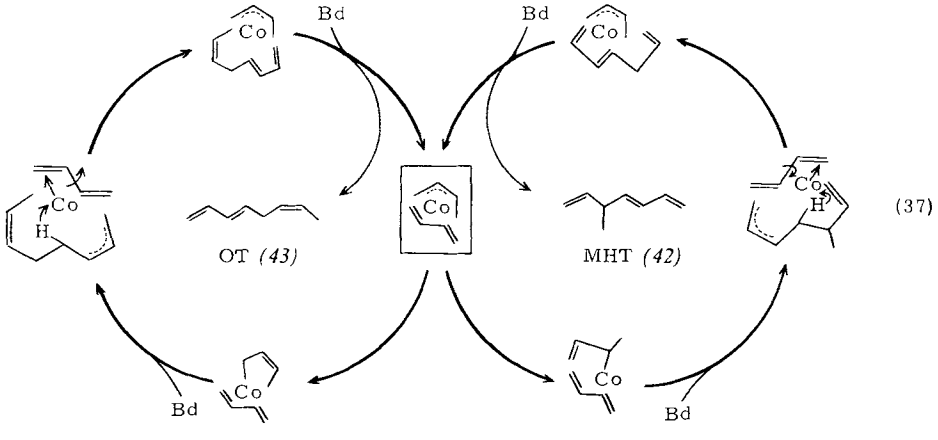
6.1. The Oligomerization of Butadiene

The ability of tris(π-allyl)cobalt to catalytically convert butadiene into open chain dimers was discovered by *Tanaka* in 1963[2]. At 20 °C 5-methyl-1,3,6-heptatriene *(42)* (MHT) and 1,3,6-octatriene *(43)* (OT) are formed with high selectivity in the ratio 9:1.

(42) *(43)*

It was shown by *Kopp*[13,14] that the butadiene displaced all three π-allyl groups [eq. (7)] and hence, using the definition suggested by *Wilke* for nickel, we are dealing here with a "naked cobalt(I)".

As can be seen from eq. (7), the stoichiometric conversion of tris(π-allyl)cobalt into the catalytically active 5-methyl-heptadienylcobalt(I) complex *(13)* is the result of a sequence of C=C insertion and β-H addition-elimination steps. Eq. (37) (Bd = butadiene) illustrates that the same processes are involved in the catalytic dimerization of butadiene on "naked cobalt".

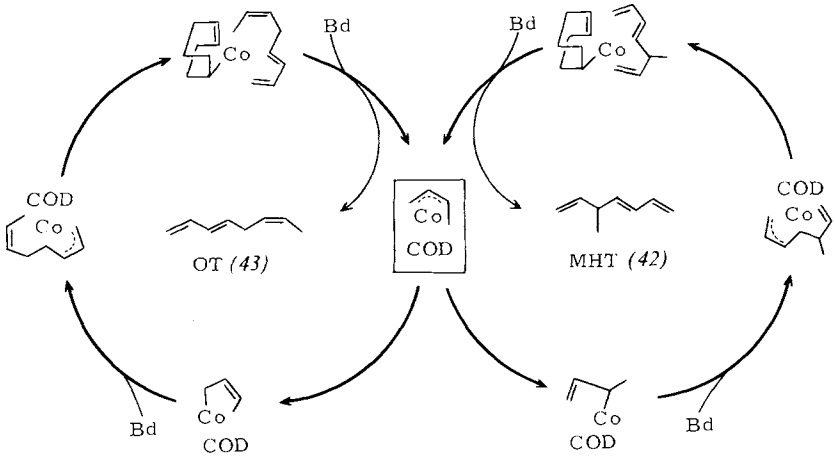


(37)

The *anti* substituted π-crotylcobalt intermediate shown in eq. (37) can be regarded as a crossing-point for the 'OT' and 'MHT' cycles: whether linear dimers *(43)* or branched dimers *(42)* are produced depends upon whether the butadiene attacks C-1 or C-2 of the crotyl group. The cyclooctenylcobalt complex *(26)* is also able to catalytically convert butadiene into the open chain dimers *(42)*

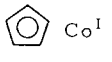
and *(43)* and can be regarded as a "modified" organocobalt-catalyst[14]. However, in this case the chelating ligand COD remains bonded to the cobalt throughout the whole of the catalytic reaction. In addition, the COD acts as the "hydrogen depot" [eq. (38)] (Bd = butadiene).

The linear dimers *(42)* and *(43)* are also 1,3-dienes and are able to react with further butadiene to give higher oligomers in a manner analogous to that shown in eq. (37) and/or (38). The formation of oligomers, using the "naked cobalt" catalysts *(1)* and *(13)* increases greatly



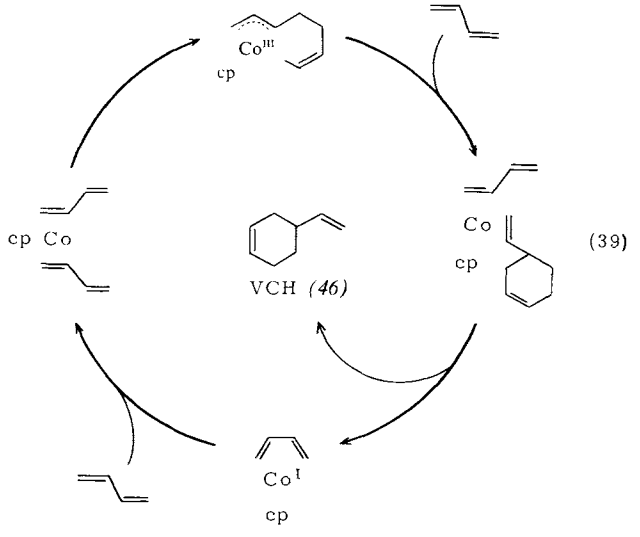
(38)

Cobalt(I) catalysts containing the π-cyclopentadienyl group as the "cycloolefin" ligand act in a completely different manner from *(1)*, *(13)* or *(26)*. The catalysis takes place on the π-cyclopentadienylcobalt moiety [*(44)* and *(45)*], without hydrogen insertion, to give cyclic dimers.

(44)  Co^I Co^I *(45)*

The derivative *(29)*, formed by transannular contraction, also belongs to the π-cyclopentadienylcobalt catalysts[20] and catalytically converts butadiene to 4-vinylcyclohexene (VCH) *(46)*[26].

The reaction is believed to occur in a manner analogous to that involving nickel[39] and an intermediate π-allyl(σ-allyl)C_8-chain bonded to cobalt may be postulated. The transition from $cpCo^{III}$ to $cpCo^I$ shown in eq. (39) corresponds to the stoichiometric conversion of *(19)* into the diene complex *(20)* [cf. eq. (17)] (cp = π-cyclopentadienyl).



(39)

when the butadiene conversion exceeds 40%. However, this effect can be suppressed by using the COD modified system *(26)* (see Table 3).

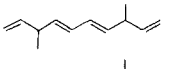
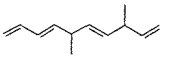
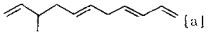
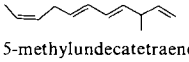
Table 3. The oligomerization of butadiene with various cobalt catalysts (60 °C and 70% conversion).

Product distribution	Catalyst *(1)/(13)*	*(26)*	*(29)*
Dimer	38% [a]	89% [a]	92% [b]
Trimer	34%	2%	—
Higher oligomers	28%	9%	8%

[a] 5-methyl-1,3,6-heptatriene *(42)* + 1,3,6-octatriene *(43)*.
[b] 4-vinylcyclohexene *(46)*.

The composition of the trimeric fraction is shown in Table 4.

Table 4. Linear trimers of butadiene. For reaction conditions see Table 3.

Compound	Amount [%]
	35%
	25
 [a]	35
	≈ 4
5-methylundecatetraene	< 1

[a] Quoted compound plus isomers.

6.2. Co-oligomerization of Butadiene with Alkenes and Alkynes

The results obtained from the oligomerization of butadiene indicate that the electivity[*] of the reaction can be

[*] The "electivity" is the ability of a catalyst to activate certain components in a mixture and cause them to react preferentially.

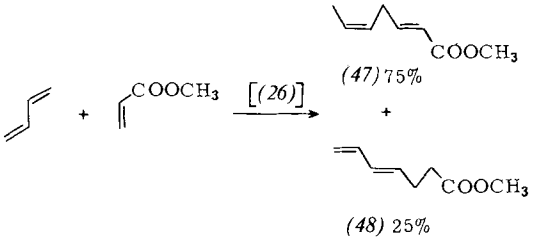
increased by modifying the "naked cobalt" catalyst (see Table 3). The difference in the electivity of *(1)*, *(13)*, *(26)* and *(29)* can be clearly seen from the results of the co-oligomerization of butadiene with alkenes. Although the simultaneous reaction of butadiene and ethylene with *(1)* or *(13)* does produce 1,*trans*-3-hexadiene and, moreover, in 97% purity, the yield of co-dimer (based on converted butadiene) is only 10%—the main product is MHT *(42)*. On the other hand, an almost quantitative codimerization to hexadiene is obtained in the presence of COD as ligand[13]. The main product using *(29)* is cyclohexene (see Table 5).

Table 5. The codimerization of butadiene and ethylene at 60 °C.

Product distribution	Catalyst *(1)/(13)*	*(26)*	*(29)*
Codimer	10% 1,3-hexadiene	98% hexadiene [a]	80% cyclohexene
Butadiene oligomers	90% [b]	2%	20% [c]

[a] 1,4-Hexadiene and 1,3-hexadiene in a 3:2 ratio.
[b] Dimer *(42)* + *(43)* and higher oligomers in a 2:3 ratio.
[c] VCH *(46)* and higher oligomers in a 9:1 ratio.

Acrylic ester can be used successfully in place of ethylene in the cobalt catalyzed co-oligomerization and similar "electivity" is observed. With *(26)* as the catalyst, the methyl esters of heptadienoic acid *(47)* and *(48)* are obtained in 96% yield[40]. The *trans*-2,*cis*-5-ester *(47)* corresponding here to the substituted *cis*-1,4-hexadiene and *(48)* to the *trans*-1,3-hexadiene. The "naked cobalt" catalysts *(1)* and *(13)* are of lower electivity, only about a 60% yield of the C_7-esters *(47)* and *(48)* is obtained—the remainder being higher oligomers.

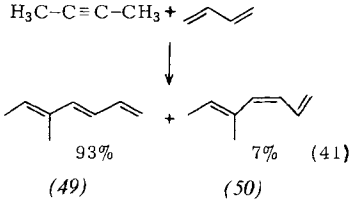


(40)

As expected, the co-dimerization using *(29)* leads, in this case, also to the cyclic products, namely methyl 4-cycloheptenoate *(46)* (60%) and VCH.

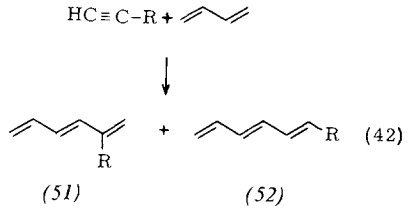
Butadiene and alkynes can be converted smoothly by *(1)*, *(13)* or *(26)* (30 min, 50 °C) into substituted hexatrienes[13,14].

The reaction of butadiene with 2-butyne yields the codimers *(49)* and *(50)* in accordance with eq. *(41)*.



(41)

In general, 1-alkynes are converted (under the same conditions) into the conjugated trienes *(51)* and *(52)* (R = *e.g.* CH_3, C_4H_9) [eq. (42)].



(42)

A side-product (*ca.* 20%) of this catalytic reaction is the cyclohexadiene derivative *(53)* a part of which is dehydrogenated to the aromatic system *(54)*.

By using the "cyclization" catalyst *(29)* it is possible to produce the six-membered ring systems *(53)* and *(54)* in pure form at 80 °C—100 °C.

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Cyclooligomerization with Transition Metal Catalysts[**]

By Paul Heimbach[*]

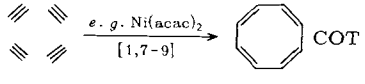
In memory of Karl Ziegler

This report is concerned not only with the syntheses of new ring systems and the preparation of derivatives of known rings but also with new types of catalysts based upon, *e.g.*, nickel, iron, molybdenum, manganese, and palladium. The broad applicability of the methylene insertion reaction as a method for identifying mono- and di-methyl-substituted eight-, ten-, and twelve-membered rings is also demonstrated. A further section is concerned with the possible mechanism of C—C bond formation in transition metal complexes; several earlier suggestions have been revised in the light of new experimental data. In addition, experimental results are discussed which indicate that the reactivity and selectivity of the complexes formed by the nickel-ligand catalyst and olefins or alkynes depend upon the structure of the ligands.

1. Introduction

At the outset of this progress report we shall briefly consider earlier catalytic ring syntheses [eq. (1)–(7)] which have been reviewed elsewhere[1–7].

As can be seen, the low-valent nickel catalysts have received particular attention [eq. (3)—(6)][***]. In several cases they have been modified to nickel-ligand catalysts by the addition of an equivalent of phosphane or phosphite (L). Reduction of the nickel in, for example, bis(pentanedionato)nickel(II) ($Ni(acac)_2$), has been carried out with organoaluminum compounds[3,17] and electrochemically[18,19]. In addition, nickel(II) alkoxides can be converted into low-valent nickel catalysts by heating them in liquid butadiene at temperatures above 80 °C whereupon, *inter alia*, an O—C coupling reaction occurs[20]. The thermal degradation of nickel(II) alkoxides was originally observed by *Meerwein*[21]. Stable nickel(0) complexes *e.g.* $Ni(CH_2{=}CH{-}CN)_2$, can also



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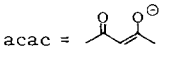

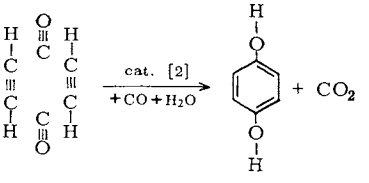

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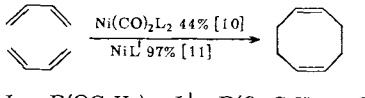


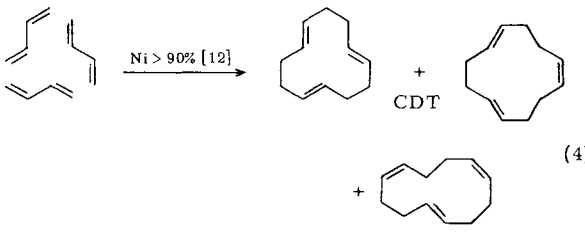
(3)

L = $P(OC_6H_5)_3$ L' = $P(O\text{-}C_6H_4\text{-}o\text{-}C_6H_5)_3$

[*] Prof. Dr. P. Heimbach
Gesamthochschule Essen and Max-Planck-Institut für Kohlenforschung
433 Mülheim-Ruhr, Kaiser-Wilhelm-Platz 1 (Germany)

[**] Based upon the work and ideas of *W. Brenner, H. Buchholz, W. Fleck, H. J. Hey, R.-V. Meyer, M. Molin, K.-J. Ploner, W. Scheidt, R. Schimpf, K.-H. Scholz, H. Selbeck, K. Tani, F. Thömel, E. Troxler, W. Wiese*, and *W. Zaar*, whose results have not as yet been published in detail.

[***] "Ni" is used to denote the nickel catalyst employed *e. g.* $Ni(COD)_2$.



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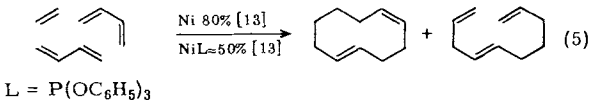

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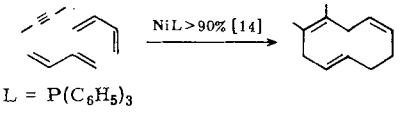

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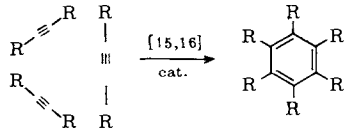
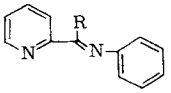


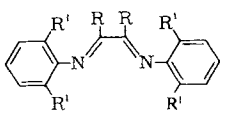
(7)

be converted into highly reactive nickel catalysts by displacement of the strongly bonded ligands with butadiene at elevated temperatures[22,23]. Similarly, the CO groups in $Ni(CO)_4$[4] or $L_2Ni(CO)_2$[10] can be more or less completely displaced. All of these various reactions produce the same catalytically active species in varying yields.

In was demonstrated for the first time in the synthesis of 1,5,9-cyclododecatriene (CDT) that, in addition to nickel, other metals *e.g.*, chromium, titanium[24], or manganese[25], could be used to prepare catalysts for the cyclotrimerization of butadiene. Likewise, the synthesis of 1,5-cyclooctadiene (COD) from butadiene is not confined to nickel-ligand catalysts[11]; the diene is also formed, although only as by-product, using bis(cyclooctatetraene)iron[26] and π-allyldicarbonyldinitrosyl iron[27]. This last catalyst yields mainly four- and six-membered rings at temperatures below 150 °C. The yield of eight-membered ring can be increased to 60% by introducing 2,2'-bipyridyl (bipy) as an additional ligand[28,29]. Other iron catalysts capable of generating cyclooctadiene have been described by two further research groups[30,31]. However, the rates of these reactions are extremely low even in the presence of the phosphanes and phosphites[31] which have proved particularly valuable as additional ligands in nickel catalysis.

Several groups have reported, essentially independently of each other, that Schiff bases having the structure shown are particularly effective additional ligands for the cyclodimerization of 1,3-dienes using iron catalysts[32-34]. In some cases the rates of reaction are greater than those involving



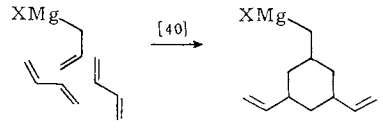


nickel-ligand catalysts of comparable selectivity. It is of interest that the cyclooctadiene formation occurs in a manner differing from that using a nickel-ligand catalyst[35]. Butadiene can also be converted into cyclooctadiene using a rhodium catalyst[36] as well as a cobalt catalyst associated with suitable ligands[37-39].

2. Recent Preparative Results in Catalytic Cyclooligomerization

2.1. New Types of Catalytic Ring Syntheses

Occasionally the term catalytic is erroneously applied to reactions in which a metal atom or -cluster or a catalyst-complex residue[*] is introduced essentially as an auxiliary group into an olefin or alkyne but is not available for further reaction. In these reactions, which can really only be regarded as being metal-induced, the metal or metal



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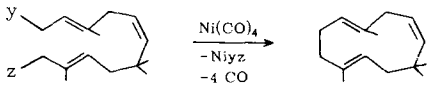
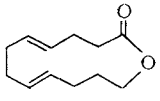


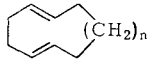
(9)

[41]

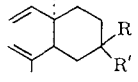
complex is employed in stoichiometric amounts. Nevertheless, such reactions have been included here where they lead to a ring system. Examples are shown in eq. (8) and (9) as well as in the syntheses of the cyclic compounds *(1)*—*(3)*.



(1) [42]



(2), n = 4, 6, 10
[43]



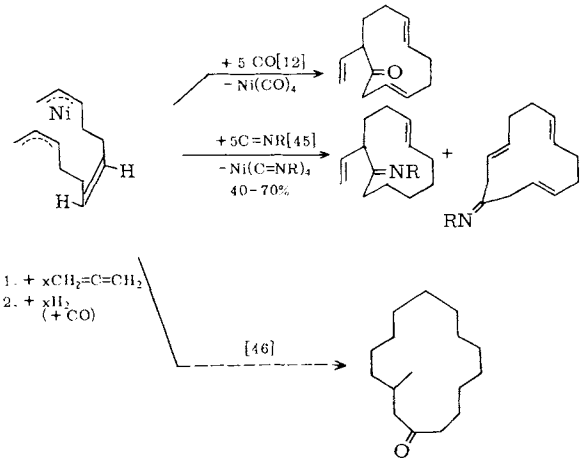
(3) [44]

Starting from a C_{12}-chain bonded to nickel (prepared from three butadiene molecules) it is possible to synthesize eleven-[12,45], thirteen-[45], and, by reaction with allene, fifteen-membered rings[46] [eq. (10)]. One or more of these reactions could probably be rendered catalytic by varying the reaction conditions or the ligand.

In the following, we consider some examples of catalytic syntheses of new ring systems. The classification is based upon *ring size*. Whereas complete conversion of butadiene [using the tri(2-biphenylyl)phosphitenickel catalyst] leads to 95% of *cis,cis*-1,5-cyclooctadiene and 4-vinylcyclohexene (2%)[**], up to 85% conversion produces the following product composition: 4-vinylcyclohexene (2%), *cis*-1,2-divinylcyclobutane (36%), and *cis,cis*-1,5-cyclooctadiene (36%)[11].

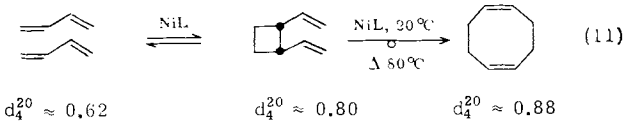
[*] The designation catalyst-complex residue is used to describe the metal and those ligands which do not play a direct role in the reaction.

[**] Unless otherwise indicated, the percentage yields are based upon the amount of olefin converted and not upon the amount initially present.



(10)

This "catalytic Cope rearrangement" is of pseudo zero order with respect to the four-membered ring and depends only upon the concentration of the catalyst and the nature of the phosphorus-containing ligand. The extensively stu-

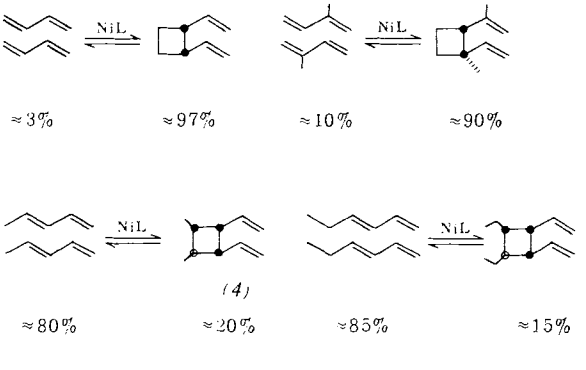


(11)

$d_4^{20} \approx 0.62$ $d_4^{20} \approx 0.80$ $d_4^{20} \approx 0.88$

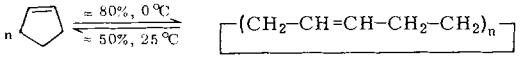
died thermal Cope rearrangement of *cis*-1,2-divinylcyclobutane is first order[48,49]. A temperature-dependent equilibrium is established between butadiene and the four-membered ring in the presence of the nickel-ligand catalyst[47].

The position of the thermodynamic equilibrium—neglecting a slight catalyst-influence—depends upon the position and nature of the substituents on the 1,3-diene (values at 30 °C)[47,50,51].



In the case of *trans*-piperylene (1,3-pentadiene)[47], as expected, the equilibrium constant at 30 °C ($K = 2.3 \times 10^{-2}$ l/mol) is found to be independent of the nature of the phosphorus-containing ligand bonded to the nickel. However, the maximum yield of *(4)* using the tricyclohexylphosphane-nickel catalyst is obtained when only 20% conversion has occurred owing to the temperature-dependent thermodynamic equilibrium. The yield decreases with further conversion because a second four-membered ring and two eight-membered rings are formed in a slow reaction.

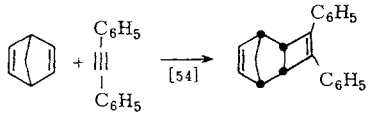
A similar dependence of the conversion (and hence of the yield based upon the initial amount of monomer) upon the temperature—arising from a reversible monomer-polymer equilibrium—has been observed by *Calderon*[52] during the metathesis of cyclopentene with molybdenum catalysts [eq. (12)].



(12)

The synthesis of divinylcyclobutane has been effected using palladium(II) salts containing anions such as ClO_4^- and BF_4^- which cannot complex with the metal[53].

The four-membered ring syntheses shown in eq. (13)—(16) have so far only been carried out with activated olefins or alkynes (MA = maleic anhydride).



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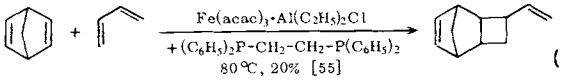

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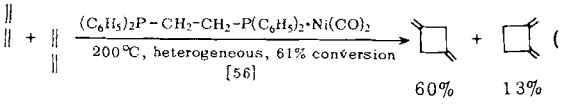

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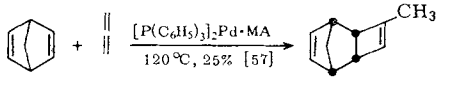
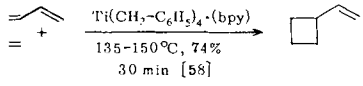


(16)

Few examples are known of the codimerization of two olefins to give a four-membered ring in a highly selective manner [*viz.* eq. (17) and (18)]. In eq. (17) butadiene, ethylene, and the catalyst (bipy = 2,2'-bipyridyl) were allowed to react in the ratio 140:180:1. A discussion of the mechanism of these catalytic, formally $(2\pi + 2\pi)$ cycloadditions is reserved for Section 3.1.



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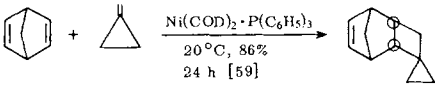
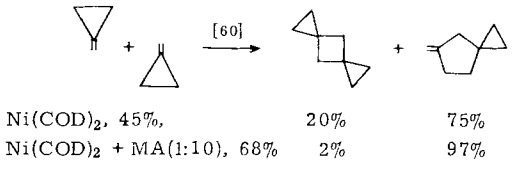


(18)

A few novel catalytic syntheses of *five-membered rings* are shown in eq. (19)—(22).

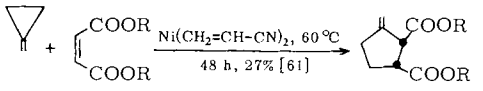
Whereas the reaction of butadiene with dialkyl-, arylalkyl-, and diaryl-substituted alkynes using a triphenylphosphanenickel catalyst gives 4,5-disubstituted *cis,cis,trans*-1,4,7-cyclododecatriene in high yield, alkyl- and aryl-substituted acetylenecarboxylic esters react with butadiene to give 5-vinyl-1,3-cyclohexadiene species *(six-membered rings)*[64,65] [eq. (23): the reaction of, *e.g.*, 2-butyne with butadiene using the same catalyst is shown in eq. (6)].

All the catalytic co-trimerization reactions leading to cyclodecatriene or 5-vinyl-1,3-cyclohexadiene species are nor-



$Ni(COD)_2$, 45%, 20% 75%
$Ni(COD)_2$ + MA(1:10), 68% 2% 97%

(19)



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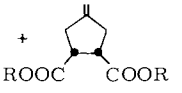

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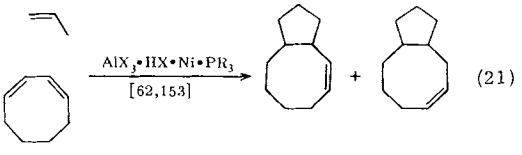

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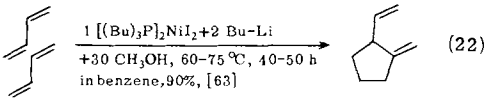

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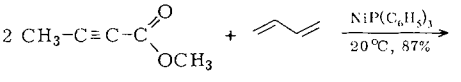

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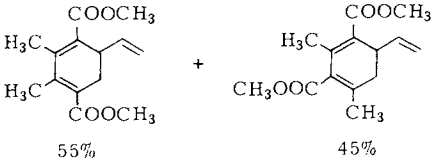

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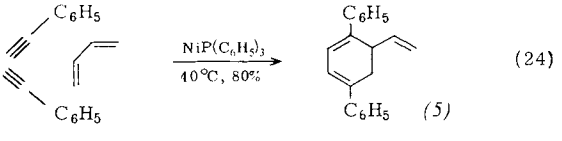


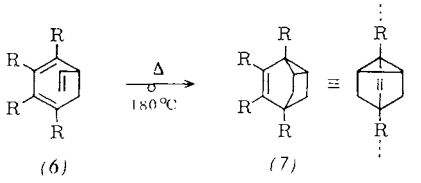
(5)

(24)

mally carried out under standard conditions: 20 °C, Ni : triphenylphosphane = 1 : 1 ; 1,3-diene : alkyne = 5 : 1 ; catalyst : 1,3-diene = 1 : 150.

In some cases, in order to maximize the yield of the desired product, it is necessary to vary both the reaction conditions and the method of addition. Thus, under the standard conditions, phenylacetylene and butadiene react to give *(5)* in only 25% yield; this can, however, be raised to 80% by adding the phenylacetylene dropwise into a butadiene-saturated solution of the catalyst in benzene at 40 °C.

Whereas the synthesis of 1,2,3,4-tetramethyl-5-vinyl-1,3-cyclohexadiene from 2-butyne and butadiene using a nickel catalyst free from phosphorus-containing ligands only gives low, often non-reproducible yields[20], *(6)* can be prepared in relatively good yield using a homogeneous $TiCl_4$—$Al(C_2H_5)_2Cl$ catalyst[66][*]. On heating to 180 °C these catalytically prepared, substituted 5-vinyl-1,3-cyclohexadiene species undergo an intramolecular Diels-Alder reaction to give tricyclooctene systems[64,65][**]. (Two other examples have also been reported[67,68].) *(7)*, R = CH_3 has a plane of symmetry. The vinylcyclohexadiene *(5)*, prepared from phenylacetylene and butadiene, has been shown in a ^{1}H-NMR investigation to be in equilibrium at 180 °C with only 30% of the corresponding trimer[64].

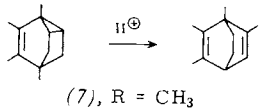


(6) *(7)*

(25)

The intramolecular Diels-Alder reaction occurs at room temperature in the presence of a heterogeneous $TiCl_4$—$AlC_2H_5Cl_2$ catalyst[66].

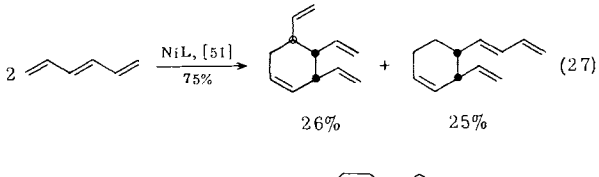
The acid-catalyzed rearrangement of the tetramethylcyclooctene *(7)*, R = CH_3[69], leads to a bicyclooctadiene system[70].



(7), R = CH_3

(26)

As well as 1,3-dienes it is also possible to react 1,3,5-trienes or a mixture of a 1,3,5-triene and a 1,3-diene with a nickel-ligand catalyst. The main products are no longer four- or eight-membered rings, but derivatives of 3,4-divinylcyclohexene. The products resulting from the reactions of *trans*- and *cis*-1,3,5-hexatriene or all-*trans*-2,4,6-octatriene with a tri(2-biphenylyl)phosphitenickel catalyst are summarized in eq. (27)—(29) (the conversions are shown beneath the arrows).



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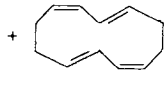

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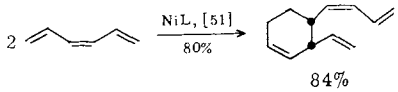
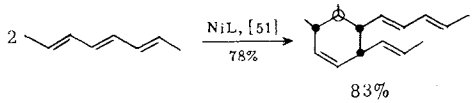


84%

(28)



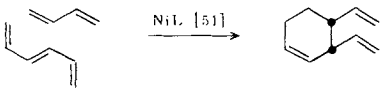
83%

(29)

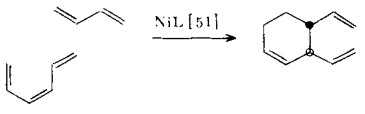
[*] In addition, the 1 : 1 codimer 1,2-dimethyl-1,4-cyclohexadiene is formed. The term "codimer" is discussed in Section 2.2.

[**] In reference [65] it is mistakenly reported that *(5f)* (instead of *(1f)*) reacts with diethyl acetylenedicarboxylate.

The codimerization of butadiene with *trans*- or *cis*-1,3,5-hexatriene occurs in over 90% yield, based on triene consumed [eq. (30) and (31)].



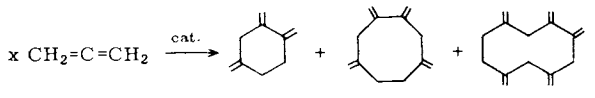
(30)



(31)

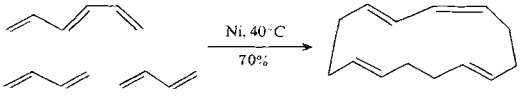
Substituted conjugated trienes react, under suitable conditions, with substituted 1,3-dienes to give derivatives of 3,4-divinylcyclohexene[51,71,72].

The catalytic cyclooligomerization of allene has been investigated by several research groups[73–75]; depending upon the reaction conditions and the catalyst, six-, *eight*-, and *ten-membered* rings can be obtained [eq. (32)].



(32)

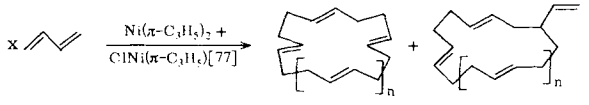
A *fourteen-membered ring* can be formed from two molecules of butadiene and one molecule of 1,3,5-hexatriene with a phosphane- or phosphite-free nickel catalyst. The yields of this simple synthesis are 70% based upon the reacted hexatriene and 40% based on reacted butadiene[72,76].



(33)

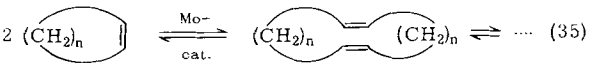
Reaction of a 30:70 mixture of *cis*- and *trans*-1,3,5-hexatriene produces a mixture of fourteen-membered rings containing 55% of the isomer shown in eq. (33).

Sixteen-membered rings can, according to *Miyake*[77], be prepared in 5—7% yield from butadiene using a mixed catalyst prepared from bis(π-allyl)nickel and allylnickel chloride [eq. (34)].



(34)

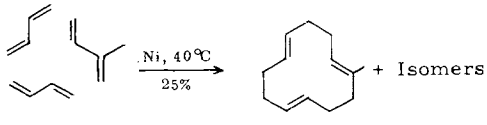
In addition to *twenty*-, *twenty-four*-, and *twenty-eight*-membered rings *etc.*, vinyl-substituted rings containing two carbon atoms less are also formed. The *sixteen*-membered ring has been prepared in up to 6% yield by *Leuchte* and *Lehmkuhl*[78] using a nickel catalyst and suitable solvent combinations. The advantage of this synthesis is that cyclododecatriene is the only side product. *Medium* and *large* rings can be prepared in up to 15% yield in a metathetic reaction using molybdenum catalysts [eq. (35)][79].



(35)

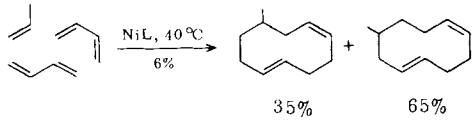
2.2. Catalytic Preparation of Methyl- and Alkyl-Substituted Eight-, Ten-, and Twelve-Membered Rings

The catalytic preparations of the above ring systems are possible using cross-oligomerization, co-oligomerization, or a combination of both. By cross-oligomerization we mean the oligomerization of unsaturated compounds of the same type but with different substituents or configuration, *e.g.*, the cyclodimerization of butadiene and isoprene (1:1) to give 1-methyl-1,5-cyclooctadiene, or the cyclodimerization of *trans*- and *cis*-piperylene (1:1) to give *cis*-3,4-dimethyl-1,5-cyclooctadiene. By co-oligomerization we mean an oligomerization of different classes of unsaturated compounds *e.g.* the cyclotrimerization of butadiene with ethylene (2:1) to give *cis,trans*-1,5-cyclodecadiene or of 2-butyne with butadiene (2:1) to give 1,2,3,4-tetramethyl-5-vinyl-1,3-cyclohexadiene. Eq. (37)–(39) summarize the yields and selectivities of some of the reactions in which a triphenylphosphitenickel catalyst has been used.



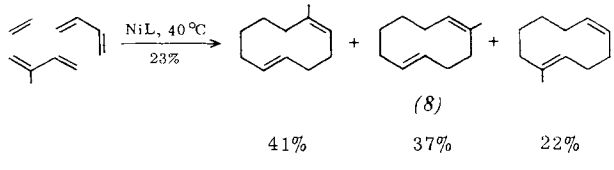
(36)

The cross-cyclotrimerization of butadiene and isoprene[81,82] is shown in eq. (36) while eq. (37) gives an example of a co-cyclotrimerization in which open-chain



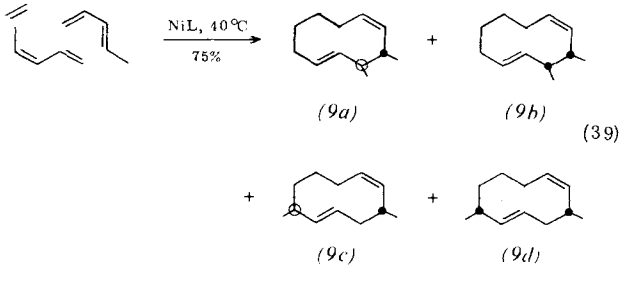
(37)

co-trimers are also formed[80]. The cross-co-cyclotrimerization of butadiene, isoprene, and ethylene is shown in eq. (38)[80,81]. The only cross-co-trimer formed using a nickel catalyst having no phosphorus-containing ligands is *(8)*.



(38)

Co- and cross-co-cyclotrimerization are observed in the reaction of a mixture of *cis*- and *trans*-piperylene with



(39)

ethylene[80]: *(9a)* and *(9d)* are formed from two molecules of *cis*- or *trans*-piperylene and a molecule of ethylene [eq (39)].

We synthesized nearly all of the possible mono- and dimethyl derivatives of the four-, six-, eight-, ten-, and twelve-membered rings for the following reasons:

1) to investigate the preparative extension of the building-block principle to nickel-catalyzed ring syntheses

2) to obtain further information on the course of reaction. The methyl group, in particular, is regarded as a perturbing group in the 1,3-diene, monoolefin, or the intermediate complexes.

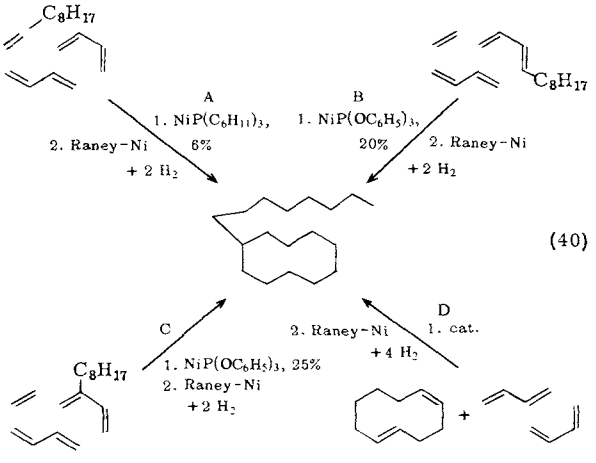
Two reactions were particularly important in determining the exact structures and configurations of the mono- and dimethyl-substituted rings:

1) the thermal[48,49] and catalytic[47,50] Cope rearrangement of 1,5-dienes, and

2) the methylene insertion reaction (Section 2.3).

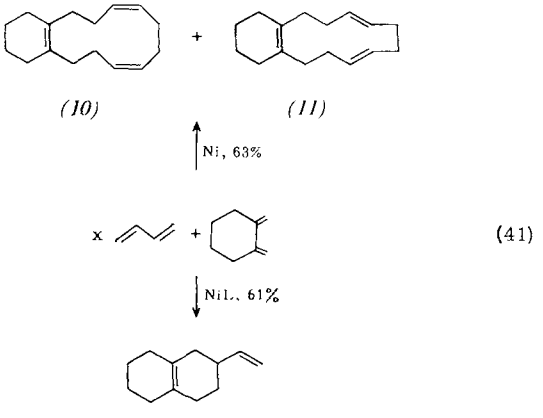
Effective and reproducible gas-chromatographic separation of the isomers is a necessary condition.

Alkyl groups larger than methyl can also be introduced into the olefin. The scope of catalytic ring syntheses utilizing the building-block principle will be illustrated for the synthesis of octylcyclodecane[13,20] as an example [eq. (40)]. The catalyst for reaction path D was $Ni(COD)_2$. The yield is 15% based upon reacted butadiene.



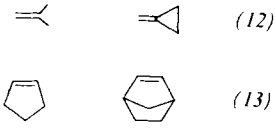
(40)

Further examples are shown in eq. (41)[82]. Compound *(10)* is the only example of a catalytically formed derivative of all-*cis*-1,5,9-cyclododecatriene.



(41)

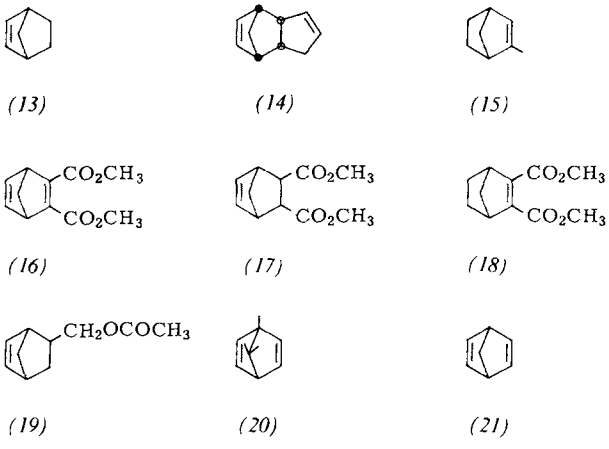
Compounds such as isobutene and cyclopentene hardly react at all in the presence of the nickel-ligand catalyst, whereas systems such as *(12)* and *(13)* are particularly reactive[83]. This obviously results in part from strain in the olefin[84].



(12)

(13)

The bicyclo[2.2.1]hept-2-ene derivatives *(13)*—*(21)* have been treated with butadiene in the presence of nickel ligand catalysts, compounds *(17)* and *(19)* were used as mixtures of *exo*- and *endo*-isomers. Derivatives of *cis,trans*-1,5-cyclodecadiene are formed. The reaction with norbornene is shown in eq. (42).

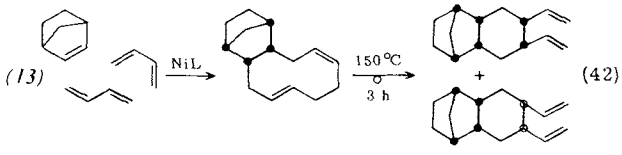


(13) *(14)* *(15)*

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

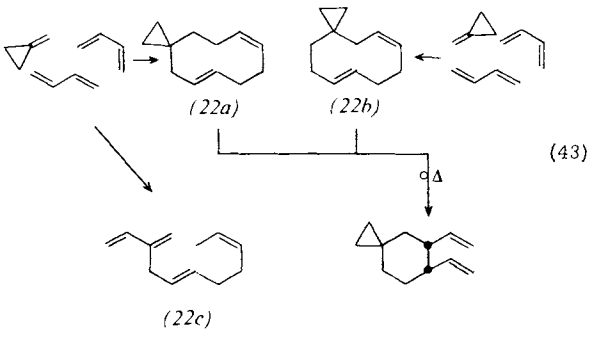
(19) *(20)* *(21)*

Only the strained double bond of dicyclopentadiene *(14)* took part in the catalytic reaction. The bicycloheptene derivatives having tri- or tetra-substituted double bonds [*e.g. (15)* or *(18)*] or subject to steric hindrance [*e.g. (20)*] cannot be co-oligomerized with butadiene. Each double bond in norbornadiene *(21)* can react individually as a monoene and both 2:1 and 4:1 adducts may be isolated.



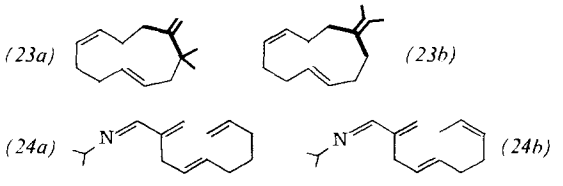
(42)

Whereas the bicyclo[2.2.1]heptene derivatives give exclusively cyclic products, the following examples show that the product distribution can be influenced to a large extent by an appropriate choice of the phosphorus-containing ligand present in the nickel catalyst. For example, the catalytic co-oligomerization of butadiene with methylenecyclopropane (for preparation see[85]) in the presence of tri(2-biphenylyl)phosphite leads predominantly to the spirododecadiene derivatives *(22a)* and *(22b)* while the use of tricyclohexylphosphane leads to 90% of the open-chain adduct *(22c)* [eq. (43)].



(43)

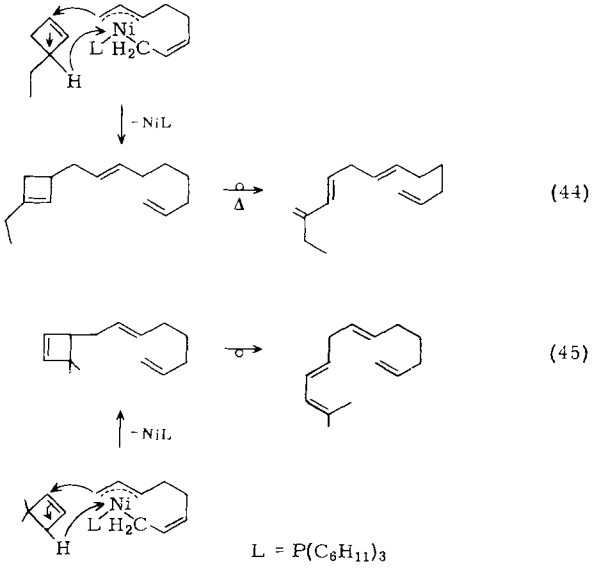
1,1-Dimethylmethylenecyclopropane[86] reacts to give, in addition to spirododecadiene compounds, the eleven-membered rings *(23a)* and *(23b)*. Similar cyclic and open-chain products to those obtained from methylenecyclopropane are also obtained by reacting *N*-isopropyl-2-methylenaziridine[87] with butadiene *e.g.* to give *(24a)* and *(24b)*[83].



The co-oligomerization of butadiene with 3-ethylcyclobutene and with 3,3-dimethylcyclobutene yields, in addition to the expected substituted cyclodecadiene derivatives, cyclobutene systems. These undergo a facile thermal rearrangement to open-chain tetraenes. The structure of the cyclobutene derivatives suggests that a different mechanism is involved [eq. (44) and (45)].

Two extreme situations can be distinguished in the cross-cyclooligomerization and the co-cyclooligomerization:

1) The molecules A and B react, independently of each other, at different rates with the catalyst in parallel reactions. In this case the difference in reactivity of A and B can be influenced by varying the concentration.



(44)

(45)

2) The molecules A and B react in different steps of a consecutive reaction. It is thus possible, for example, that B is only able to react with the catalyst after this has been modified by reaction with A. Nevertheless, a reversal of the reaction sequence can, in a few cases, be effected by the introduction of substituents into A and/or B (see *e.g.* eq. (6) and (23); further examples will be discussed in ref. [88]).

2.3. The Methylene Insertion Reaction

The usefulness of the methylene insertion reaction in the identification of catalytically formed mono- and di-methyl derivatives will be illustrated for 1- and 3-methyl-1,5-cyclooctadiene. Approximately 2% of diazomethane (the low concentration enables double or multiple reaction to be avoided) is dissolved in 1- and/or 3-methyl-1,5-cyclooctadiene. Irradiation with a mercury-vapor lamp causes the formation of singlet methylene which inserts in an essentially statistical manner into the C—H bonds (for this reason this methylene has been described by one American as "the most democratic reagent in organic chemistry"). At the same time reaction with the double bonds leads to cyclopropane derivatives; these can also be prepared by heating 1- or 3-methylcyclooctadiene with diazomethane in the presence of copper powder[89] and hence be identified in a mixture of methylene insertion products. A particular advantage of the method is that the structure and configuration of the original olefin are maintained[*][81].

This reaction of diazomethane was originally discovered by *Meerwein*[90] and exploited specifically for the identification of the next higher homologs by *von Doering*[91], *Dvoretzky*[92], and in particular *Schomburg*[93].

By reacting the methylene with 1- and 3-methyl-1,5-cyclooctadiene, it proved possible to prepare a mixture containing small amounts of all the dimethyl- and ethyl-derivatives of *cis,cis*-1,5-cyclooctadiene and to then determine their retention indices in capillary columns. Further identi-

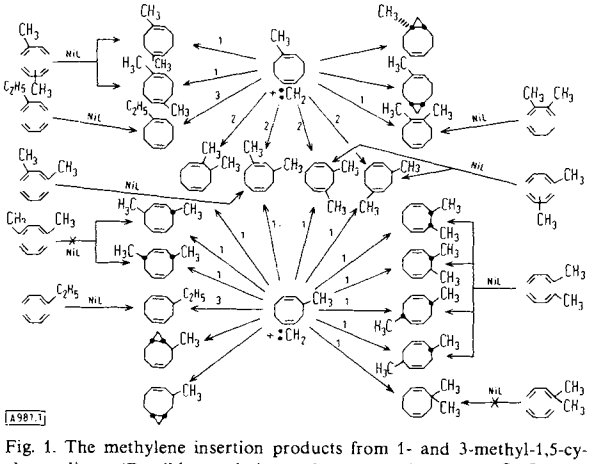


Fig. 1. The methylene insertion products from 1- and 3-methyl-1,5-cyclooctadiene. (Possible catalytic syntheses are also shown [81].) The number on the arrows show the statistical weight with which the isomers can be expected to be generated.

[*] Difficulties in the application of the methylene insertion reaction have so far only been experienced with *cis*- and *trans*-hexatriene. Isomerization of the triene could be avoided by using a filter which absorbs the radiation up to a wavelength of 300 nm [72].

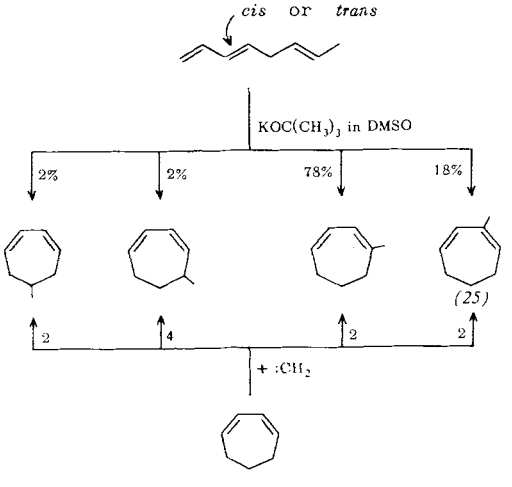
fication followed by chemical means and by comparison with the catalytically formed products (Fig. 1).

A brief explanation is appropriate. For example, only four isomers are common to both the methylene insertion reactions into 1- as well as into 3-methyl-1,5-cyclooctadiene; of these, 1,4- and 1,7-dimethylcyclooctadiene can be prepared catalytically by the cross-dimerization of isoprene and piperylene, and 1,3-dimethylcyclooctadiene by the cross-dimerization of butadiene with 2-methyl-1,3-pentadiene. Hence the fourth isomer can only be 1,8-dimethylcyclooctadiene. In addition, it can be deduced that, for example, catalytically synthesized, eight-membered dimers of isoprene can only be produced by methylene insertion reaction from 1-methylcyclooctadiene and those of piperylene only from 3-methylcyclooctadiene, in complete agreement with the experimental results.

An initially unanswered problem was that of the assignment of the two methyl groups in the 3,4-, 3,7-, and 3,8-positions of 1,5-cyclooctadiene. Their *cis*- or *trans*-arrangement were established indirectly by, *inter alia*, use of the Cope rearrangement of the corresponding four-membered rings[47] and by a ^{1}H-NMR study of the $PdCl_2$ complexes formed by the eight-membered rings[94]. Structural information was also frequently obtained from the retention behavior of the isomers[95].

In a similar manner we determined the structure and configuration of the mono- and di-methyl derivatives of *cis*, *trans*-1,5-cyclodecadiene, *cis*-1,2-divinylcyclohexane, *trans*-1,4,9-*n*-decatriene[80,81], of *trans,trans,trans*-, *trans,trans, cis*-, and *trans,cis,cis*-1,5,9-cyclodecatriene[81,82] as well as the trimethyl derivatives of *cis*- and *trans*-3,4-divinylcyclohexene formed by reaction of all-*trans*-2,4,6-octatriene with methyl-substituted 1,3-dienes[51,71]. All the 1,2-, 1,3-, 1,4-, 1,5-, 1,6-, and 1,7-dimethyl derivatives of cyclododecane could be assigned in pairs[81,82].

Isomerization of the octatrienes, which can be readily prepared from butadiene using an amine-modified nickel[96,97] or palladium[98,99] catalyst, leads preferentially to two of the four methyl-1,3-cycloheptadiene isomers. *Zuech et al.*[100] and *Kloosterziel et al.*[101] employed amides as the catalyst. However, better results were obtained using potassium *tert*-butoxide in DMSO[102] at 60 °C[103] [eq. (46)].



(46)

Good yields of 1-methylcycloheptene can be obtained by partial hydrogenation[20].

All four isomers of methylcycloheptadiene could be identified quickly and without isolation by using a combination of methylene insertion reactions (statistical weight of the resulting isomers and retention behavior) and a study of the maleic anhydride (MA) adduct of *(25)*. As can be seen from this last example, *seven-membered rings* can be easily prepared using a combination of catalysis and ring-closure isomerization.

3. Mechanism of C—C Bond Formation in Transition Metal Complexes

The following section is devoted to a discussion, in simple, understandable terms, of the similarities shared by the various reactions.

Two review articles[104,105] by *Nyholm* deal, from the standpoint of an inorganic chemist, with the main factors determining the structure and reactivity of a complex. Reviews dealing with individual aspects are also available[6,106-117].

In the following, special attention has been given to the problems associated with symmetry control.

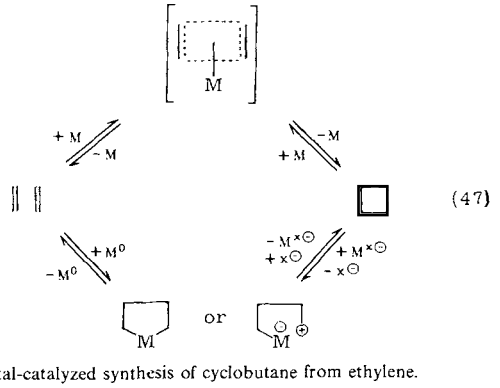
3.1. Symmetry Control in Metal-Catalyzed C—C Bond Formation

The synthesis of four-membered rings (a simple reaction to carry out catalytically) has during the last few years become the topic of a scientific controversy. According to the Woodward-Hoffmann rules[118], [2π-2π]-cycloadditions as a suprafacial process are thermally forbidden but photochemically allowed. According to a hypothesis developed by *Mango* and *Schachtschneider*[119,120] ("forbidden-to-allowed catalysis") these processes become allowed in a metal complex because d orbitals of appropriate symmetry are able to accept and donate electrons. The authors neglect to take into account the following variables which influence the MO scheme and hence the correlation possibilities:

1) the geometry of the transition state,

2) the number of electrons,

3) other ligands on the metal.



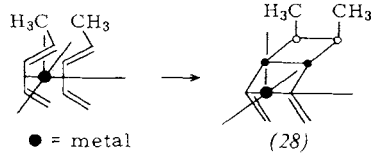
(47)

Fig. 2. Metal-catalyzed synthesis of cyclobutane from ethylene.

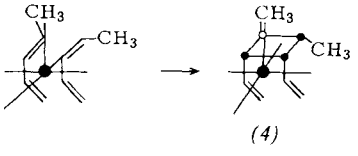
For these reasons the MO scheme must be calculated[121-123] or, where possible, backed by experimental evidence[124,125] (for difficulties see refs. [125–127]).

The approach developed by *Mango* and *Schachtschneider* has been used, in some cases with fundamental alterations, by other authors[128-130]. In Figure 2 we show an alternative mechanism for this reaction which is supported by the experimental results.

The extension of the hypothesis developed by *Mango*[131] for the metal-catalyzed formation of *cis*-1,2-divinylcyclobutane from butadiene to piperylene produces the situation shown in eq. (48) (concerted reaction). However, in contrast, *(28)* is formed by the reaction of one molecule each of *cis*- and *trans*-piperylene and *(4)* is formed from two molecules of *trans*-piperylene. We believe that the reaction pro-



(48)



ceeds in a stepwise manner in which each step, *i.e.*, the cyclization to a metalaring[132] is a concerted process.

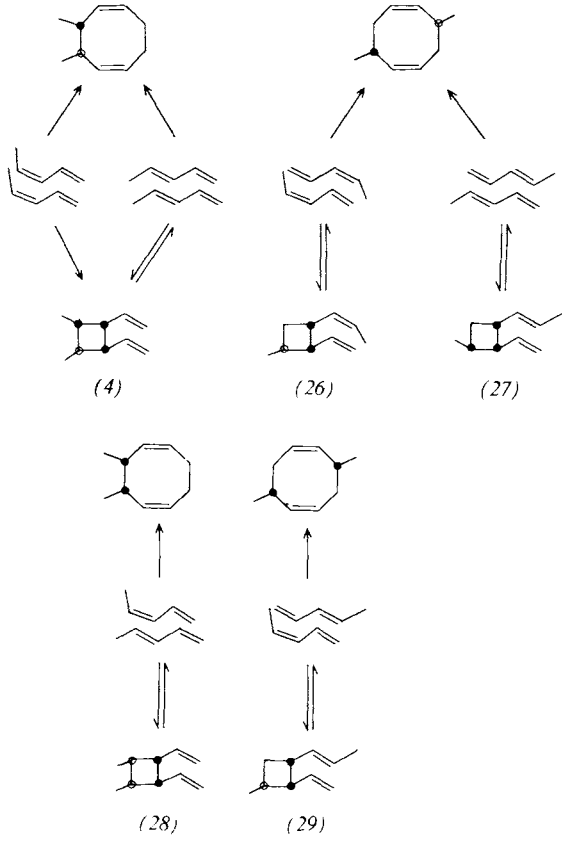
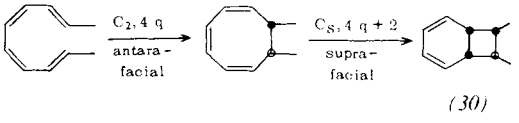


Fig. 3. Formation of four- and eight-membered rings from *cis*- and *trans*-piperylene using a nickel-ligand catalyst[47].

Figure 3 illustrates the stereochemical relationships in the formation of four- and eight-membered rings from two molecules of *cis*- or *trans*- as well as from one molecule each of *cis*- and *trans*-piperylene.

The assignment was initially complicated by an isomerization of *cis*-piperylene to *trans*-piperylene which could occur *via*, for example, the four-membered ring *(4)*[*]. The stereochemical course of reaction can, however, be established with certainty by cleaving the four-membered rings into *cis*- or *trans*-piperylene on a tri(2-biphenylyl)phosphite-nickel catalyst at 50 torr. The 1,3-diene produced (in addition to the eight-membered ring) is immediately removed from the reaction mixture and hence does not isomerize (a reaction which could proceed through the intermediacy of *(4)*).

At a first glance it seems contradictory to propose that the catalytic four-membered ring synthesis proceeds in a stepwise manner and that each step is a concerted symmetry-controlled process. The synthesis of a four-membered ring from *trans,cis,cis,trans*-2,4,6,8-decatetraene described by *Huisgen et al.*[133] can be introduced to illustrate this point [eq. (49)].



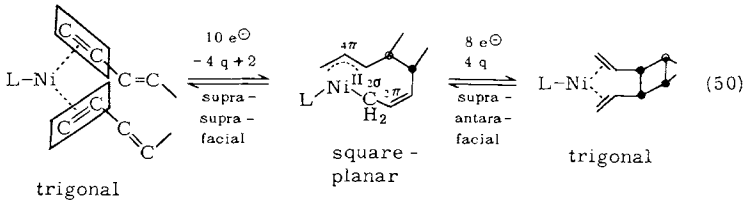
(49)

In analogy to this we suggest that the first step in the formation of *(4)* occurs in a supra-supra-facial manner ($10\,e^- = 4$ electrons from each 1,3-diene + 2 electrons from the metal = (4q + 2) process) and the second in a supra-antara-facial manner ($8\,e^- = 4$ electrons from the π-allyl group + 2 electrons from the Ni—C bond + 2π-electrons from the double bond). The same result would be obtained if an antara-antara-facial step were followed by an antara-supra-facial step. However, in this case the methyl groups in the C_8-chain would occupy axial instead of equatorial positions.

According to this approach the C—C bond formation occurs outside the complex sphere; the necessary redox-process occurring within the complex sphere (concerning "formal redox-processes" see refs. [3, 5]).

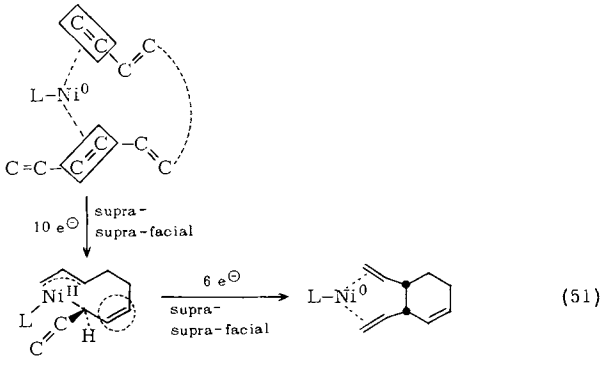
As far as the stereochemistry of *(30)* and *(4)* is concerned, it is of no consequence whether the four-membered ring is formed in a thermal or a catalytic reaction. The two reactions differ in that in the first step of the catalytic C—C bond formation, the metal contributes two electrons to the π-system. In the case of the thermal formation of the four-membered ring, symmetry control is the result of direct conjugation (the two "*trans*-piperylene" moieties are joined by a C—C σ-bond) while in the catalytic reaction, symmetry control is the result of coupling of the piperylene molecules through the metal. Stepwise reaction mechanisms are also proposed for both the rearrangement of the highly strained molecule cubane[134] (see below) as well as for the cyclodimerization of piperylene for which only a small thermodynamic driving force exists.

[*] Isomerization of *cis*- to *trans*-piperylene which occurs during the formation and cleavage of the C_8-chain (which is perhaps faster) is neglected here.



(50)

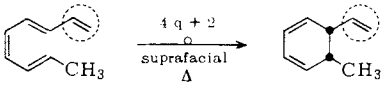
Non-involvement of the circled *cis*-double bond in complex *(31)* [eq. (51)] in the oxidative C—C bond formation[*] (2 electrons less, (4q+2) process) leads to a supra-supra-facial reaction. In agreement with experimental results and the reactions course as suggested by models, *cis*-3,4-divinylcyclohexene is formed from butadiene and *trans*-1,3,5-hexatriene and *trans*-3,4-divinylcyclohexene from butadiene and *cis*-1,3,5-hexatriene (*e.g.* $6e^- = 4$ electrons from the π-allyl group + 2 electrons from the Ni—C bond = (4q+2) process).



(51)

(31)

The additional vinyl group accelerates the reductive C—C bond formation without being directly involved as a π-system in the rearrangement. This should be compared with the thermal ring-closure reaction shown in eq. (52).

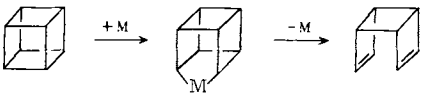


(52)

Symmetry-allowed rearrangement in a ligand system must correspond to symmetry-allowed processes at the metal (see for example ref. [134]).

Finally, we should mention that the correlation found for the initial C—C bond formation during the cyclodimerization of piperylene also applies to dimethyl-substituted *cis,trans*-1,5-cyclodecadiene[80,81] and *cis*-3,4-divinylcyclohexene[51,71].

A stepwise reaction mechanism has also been postulated by other authors. For example, *Cassar*, *Eaton*, and *Halpern*[135] could show that the highly strained molecule cubane reacts in the presence of a rhodium complex to give *syn*-tricyclooctadiene *via* a metalacyclopentane system [eq. (53)].



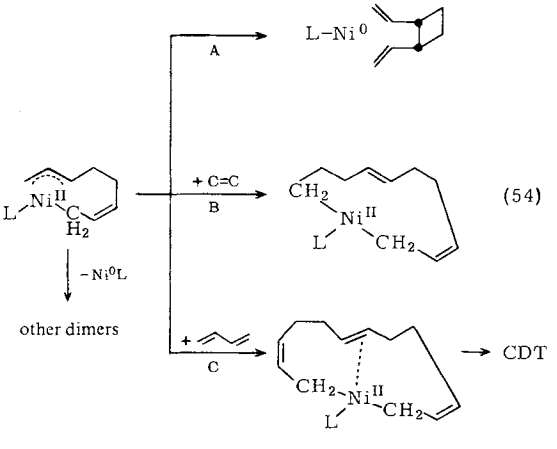
(53)

Recently, it has been possible to show that a metalacyclopentane compound is formed as an intermediate (X-ray results and chemical conversion to a cyclobutane derivative) in the formation of a four-membered ring system from the iridium-catalyzed cyclodimerization of bicycloheptadiene[136]. The proposition that the ring-closure reaction occurs in a stepwise manner does not allow any conclusions to be drawn concerning the implementation of the symmetry rules to metal-catalyzed reactions.

3.2. Further General Considerations

In the preceding section, we have assumed that the stepwise formation of *cis*-1,2-divinylcyclobutane occurs in a redox process involving the central metal atom and the ligands: the first step involves oxidation of the zerovalent metal (reductive C—C bond formation) and the second step reduction of the metal (oxidative C—C bond formation).

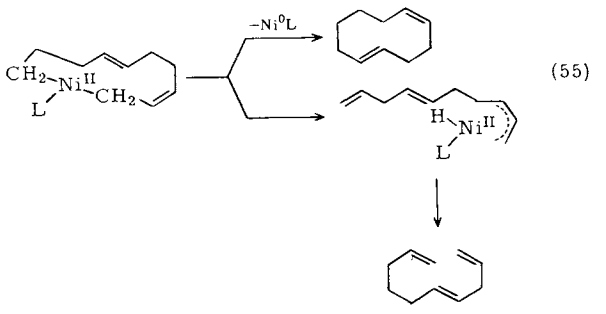
A spontaneous redox process between the metal and the ligands accompanied by an alteration in the arrangement of the ligands has been investigated for cobalt complexes by *Collman et al.*[137] using IR techniques (see also ref. [165]).



(54)

A number of nickel-catalyzed processes are, however, known which lead to C—C or C—H bond formation and which do not involve a change in the oxidation state of the metal, *e.g.* nucleophilic ligand exchange on Ni(II) and electrophilic ligand exchange on Ni(0). These reactions are in competition with each other and which process actually occurs will depend upon the complete ligand field. Particularly interesting are those cases in which only one parameter is altered. Thus, *Tolman*[138] has correlated the electronic effect of phosphanes and phosphites in $LNi(CO)_3$

[*] The terminology reductive or oxidative C—C bond formation as well as nucleophilic or electrophilic ligand exchange used by the author, refer to that bond in the hydrocarbon which is involved in the reaction (see Section 3.2).

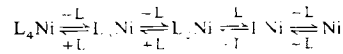


(55)

complexes with the $\nu_{CO}(A_1)$ frequency. We shall discuss this electronic effect associated with the ligand using as examples the nickel-catalyzed co-oligomerization of butadiene and ethylene, and also part of the process leading to the co-oligomerization of isoprene with ethylene. The first step here is the formation, from the 1,3-diene, of a C_8-chain bonded to nickel (the ethylene reacts only after oxidation of the metal has occurred) (Fig. 4).

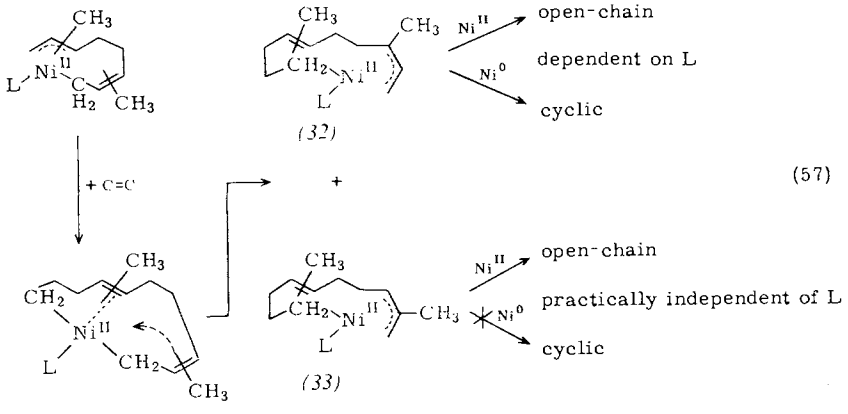
The electronic situation created by the ligands determines whether the simultaneous presence of, for example, ethylene and butadiene cause the next step to be attack of the disubstituted double-bond (reaction A), or the attack of ethylene with nucleophilic ligand exchange (reaction B), or attack by butadiene (reaction C) [eq. (54)]. It can be seen from eq. (55) that the C_{10}-chain which is produced (similar to eq. (54) (reaction B)) either undergoes oxidative C—C bond formation to give *cis,trans*-1,5-cyclodecadiene or nucleophilic exchange followed by oxidative C—H bond formation to give 1,4,9-decatriene.

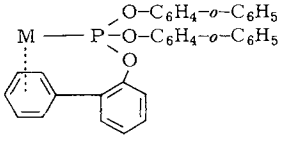
In the case of tri(2-biphenylyl)phosphite steric effects can also be of importance and hinder both the entry of further ligand molecules and disproportionation of the complex in the sense shown in eq. (56)[139]. In addition a chelate effect (and associated electronic effect) is possible with this ligand.



(56)

The formation of open-chain and/or cyclic dimethyl-C_{10}-compounds during the co-dimerization of isoprene with ethylene is dependent upon the nature of the phosphane or phosphite and/or the position of the methyl-group in the π-allyl system [eq. (57)]. The position of the methyl group in *(33)* favors the Ni(II) configuration to such an extent that open-chain products are formed almost exclusively. On the other hand, in *(32)* the formation of open-chain or cyclic products is a function of the electronic character of the ligand L.





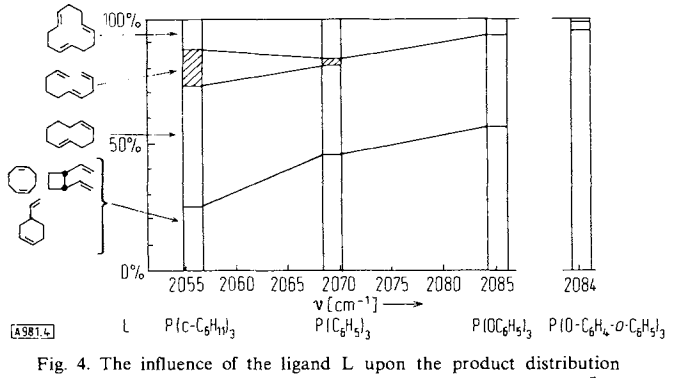
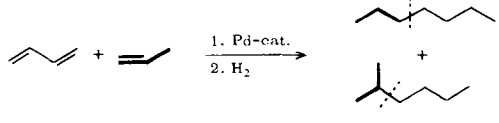


Fig. 4. The influence of the ligand L upon the product distribution in the LNi-catalyzed co-trimerization of butadiene and ethylene [see eq. (54) and (55)]. The $\nu_{CO}(A_1)$ frequency of the $LNi(CO)_3$ complexes has been chosen as a measure of the electronic effect of the ligand (the more C_{10}-compounds produced the greater is the proportion of open-chain C_{10}-compounds [13]). Reaction conditions: 40 °C. Molar ratio butadiene: ethylene = 1 : 1.

The formation of the *iso*- and *n*-heptane skeleton during the co-dimerization of butadiene with propylene using a phosphane- or phosphite-containing allylpalladium-chloride-AlX_3 catalyst[140], is also dependent upon the nature of the ligands [eq. (58)].



(58)

The effect of the ligand in complex *(32)* can be attributed to a preferred formation of a Ni(0) complex (oxidative C—C bond formation to give cyclic compounds) or a Ni(II) complex (nucleophilic ligand exchange = β-H-elimination in *(32)* followed by oxidative C—H bond formation to give open-chain compounds).

The formation of the iso- or *n*-heptane skeleton can be attributed to a ligand-dependent nucleophilic or electrophilic attack on the complex by the propylene. The HOMO

and LUMO coefficients for propylene, according to a CNDO calculation, have the following values (the square of the coefficients is a measure of the electronic density[*]).

	C-1	C-2	1 2
LUMO	0.68	−0.72	CH=CH—CH_3
HOMO	0.71	0.63	

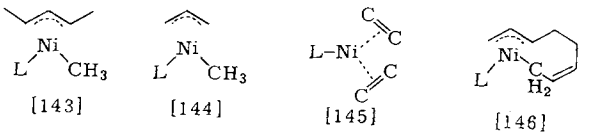
These values make it understandable that C-1 prefers to attack the metal in a nucleophilic and C-2 in an electrophilic manner. This type of argument is based upon the principles of the frontier-orbital theory developed by *Fukui*[141] in which electron-acceptor or -donor interaction occurs preferentially at that position which has the highest value for the square of the coefficient in the HOMO (highest occupied molecular orbital) or the LUMO (lowest unoccupied molecular orbital) (for a review see ref. [142]).

It would probably be worthwhile to attempt to use the frontier-orbital theory to predict the reactivity (initially qualitatively) of olefins in metal-catalyzed processes. Drastic assumptions are necessary and we are at present testing the relevance of the qualitative predictions obtained[20].

4. Prospects

An attempt has been made in this progress report to indicate some common aspects of metal-catalyzed reactions. In particular, we have tried to show that the metal complexes not only act as suitable matrices by causing the reaction to occur in one particular spatial arrangement but can also be profitably regarded as auxiliary substituents which are introduced into the π-system, thereby reinforcing or reversing its electrophilic or nucleophilic character. The metal complex is of particular value, as an auxiliary substituent since changes in the electronic configuration can cause a reversal in behavior during the individual bond-formation steps. The introduction of additional ligands on the metal provides another variable.

Many investigations are necessary in order to obtain an understanding of a catalytic process. For example, a series of reactant-, product-, and intermediate complexes have been isolated and their behavior studied[143–147].

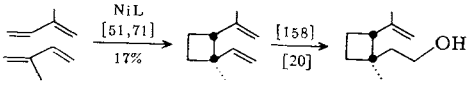


[143] [144] [145] [146]

Kinetic and competition experiments have also been used to investigate, for example, whether an isolated intermediate complex is relevant to the main- or side-path of the reaction or whether a reaction is kinetically or thermodynamically controlled.

An important point has, however, been completely neglected. There is an almost complete absence of thermodynamic data for alkylmetals and allylmetals to mention just two classes of compounds (see for example refs. [106, 148]).

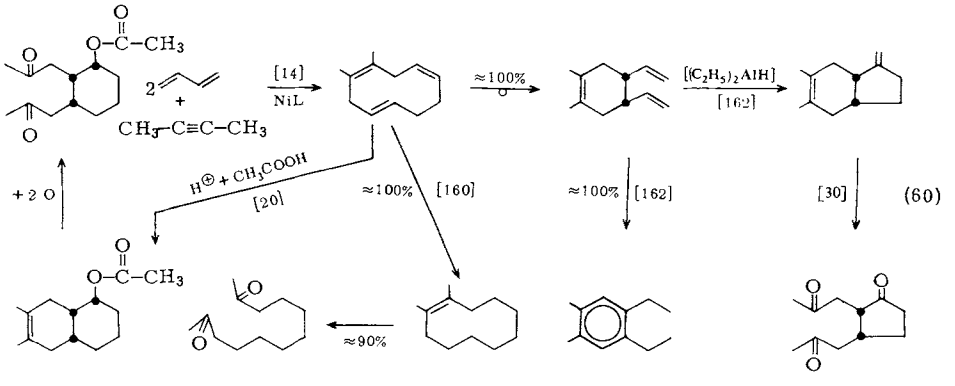
In the past the main interest in metal-catalyzed reactions has centered on petrochemical processes such as the production of aldehydes and alcohols[149,150], acetaldehyde[151], C_{12}-dicarboxylic acids or lactams[152], olefins[153,154], and α-olefins[155–157]. However, we expect that in the future there will be an increase of interest in the preparation of fine chemicals in general—particularly by the perfumery and pharmaceutical industries. Catalysis may also be expected to be used in the partial syntheses of natural products (*e.g.* terpenes from isoprene). An example is the two-step synthesis of the sex attractant of the boll weevil [eq. (59)][158,20]. The first step is metal-catalyzed and the second (addition of >B—H followed by oxidation) is metal-induced.



(59)

A large variety of products will also become available from organic syntheses using catalytically formed compounds as starting materials. This possibility has been thoroughly investigated, for example, in the case of the 4,5-disubstituted-*cis,cis,trans*-cyclodecatriene system [eq. (60)][76,154–162].

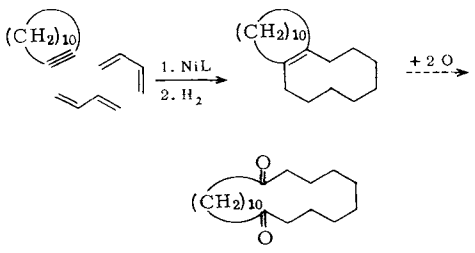
A wide variety of mono- and dialkynes have been reacted in addition to 2-butyne. A ring-expansion sequence has been developed using cyclic alkynes, *e.g.* the expansion



(60)

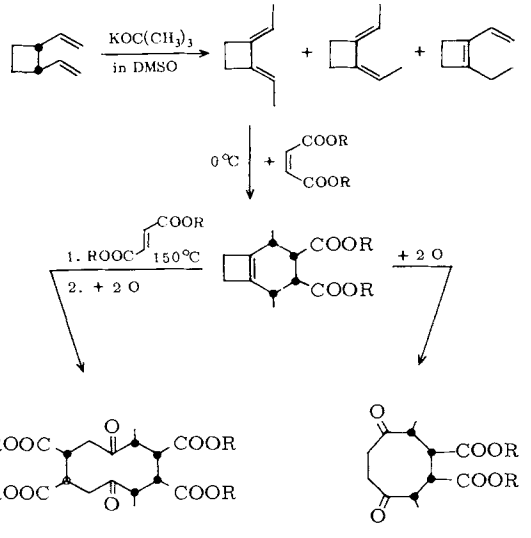
by eight C-atoms shown in eq. (61), by a combination of catalytic and stoichiometric reactions[163].

[*] The calculations were kindly carried out by Dr. *F. Mark*.



(61)

A number of interesting syntheses have likewise been carried out starting from *cis*-1,2-divinylcyclobutane. A few examples are shown in eq. (62)[164].



(62)

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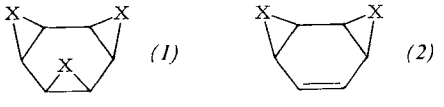
COMMUNICATIONS

cis-Triazatris-σ-homobenzene (*cis*-"Benzene Triimine")[**]

By *Reinhard Schwesinger* and *Horst Prinzbach*[*].

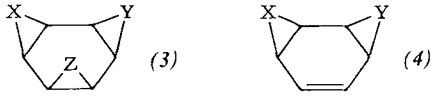
Directed nucleophilic substitutions of *cis*-trioxatris-σ-homobenzene (*cis*-"benzene trioxide")[1a] have given access to a series of potential precursors for the synthesis of aza-, thia- and phospha-analogous compounds *(1)* and the related bishetero-bishomobenzene systems *(2)*[1b].



(1) *(2)*

X = —O—, —NR—, —S—, —PR—, —CR^1R^2—

New possibilities also open up for construction of carbocyclic[2] and mixed *cis*-tris- and *cis*-bis-σ-homobenzene derivatives *(3)*[3] and *(4)*[4]. Here we describe the preparation



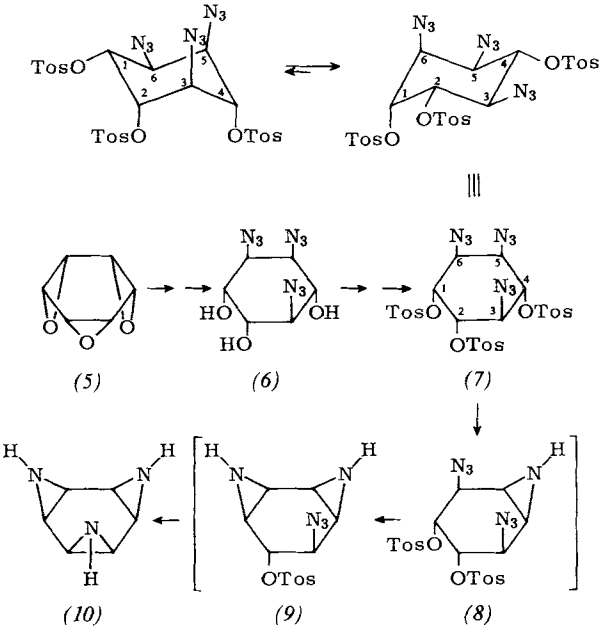
(3) *(4)*

X,Y,Z = —O—, —NR—, —S—, —PR—, —CR^1R^2—

of *cis*-triazatris-σ-homobenzene (*cis*-"benzene triimine"; 3,6,9-triazatetracyclo[6.1.0.$0^{2,4}$.$0^{5,7}$]nonane) *(10)* as the first example of such syntheses starting from *cis*-"benzene trioxide" *(5)*[5].

Reaction of *(5)* with six equivalents of NaN_3 in $MgCl_2$-buffered methanol (65 °C; 48 h) affords crystalline 3,5,6-triazido-1,2,4-cyclohexanetriol *(6)* in 98% yield; tosylation thereof with 4.5 equivalents of *p*-toluenesulfonyl chloride (pyridine, 20 °C, 14 days) gives the triester *(7)* in almost quantitative yield. The *chiro*-inositol configuration is proposed for *(6)* and *(7)* because of the behavior of *(5)* with univalent nucleophiles[1b] and is proved unambiguously by ^{1}H- and ^{13}C-NMR analysis of *(7)*. Here it is noteworthy that once more[1b] all the cyclohexane-protons and -carbon atoms can be assigned on the basis of heteronuclear double resonance experiments (Table 1)[6].

Three-fold reduction and elimination to give *(10)* can be achieved in one operation by known procedures[7] (4.5 mol of $LiAlH_4$, tetrahydrofuran, 20 °C, 10 min). We have not found any indication of formation of isomeric by-products. The specificity of the reaction makes it probable, for steric reasons and as required by our working hypothesis, that the equatorial azide group on C-5 of *(7)* is reduced first and that after inversion the monoaziridine *(8)* is the primary product, although it has not yet been isolated.



(5) *(6)* *(7)* *(10)* *(9)* *(8)*

The geometry and symmetry of *(8)* allow the sole route leading to *(10)* by way of *(9)*[8].

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The triimine *(10)* separates from CH_2Cl_2 as colorless crystals [45% yield calculated on *(5)*: not optimized]; it is very readily soluble in water or methanol, less readily in ethanol and sparingly in methylene chloride, chloroform, acetonitrile, acetone or tetrahydrofuran. *(10)* is thermally stable up to *ca.* 150 °C; when heated rapidly to *ca.* 200 °C it explodes.

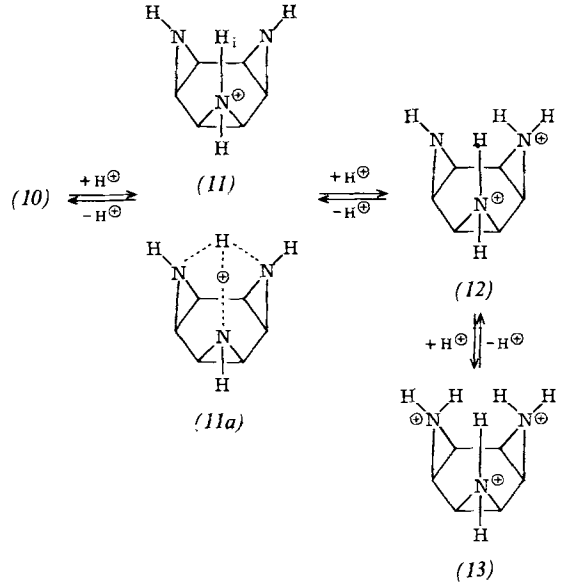
For the singly *(11)* and doubly *(12)* protonated compounds in aqueous perchloric acid we obtained the pK_a values 6.42 and 2.71 (20 °C), respectively. A pK_a value of *ca.* −1.0 can then be calculated for the trication *(13)* by extrapolation, but the true value is probably lower owing to steric compression of the three inner hydrogen atoms. The $N \cdots H_{inner}$ distance (*ca.* 2.35 Å) and the good agreement of the measured pK_a values for *(11)* and *(12)* with those estimated by means of model compounds make it improbable that the conjugated acid *(11)* profits significantly from a delocalization of the inner proton in the sense of *(11a)*[11].

Comparison with aziridine discloses no unusual features in the UV, ^{1}H- or ^{13}C-NMR or IR data of *(10)* (Table 1), due to the special relative arrangement of the three aziridine rings in the latter; and in this respect trioxa-*(5)* and triaza-σ-trishomobenzene *(10)* behave similarly. This similarity is emphasized by the mass spectra of *(5)* and *(10)* which show much correspondence in their fragmentation pattern and relative intensities (Table 1)[14].

Table 1. Physical properties of compounds *(6)*, *(7)* and *(10)* [a].

Cpd. M. p. [°C]	UV [b] λ_{max} [nm] (ε)	^{1}H-NMR τ	J [Hz]	^{13}C-NMR [ppm]
(6) 142 (dec.)	281 (80)	4.80 (br.s; 1 OH)		63.9 }
		5.35 (br.s; 2 OH)		64.4 } C-3, C-5, C-6
				68.8 }
		5.8–6.5 (m, 6 H)		70.5 }
				71.4 } C-1, C-2, C-4
				72.6 }
		[c]		[c]
(7) 154–155	274 (1850)	2.1–2.7 (m, 12 H)		146.3; 145.9; 145.3;
	263 (2300)	7.51 (s, 2 CH_3)		133.9; 132.0; 131.6;
	227 (35500)	7.56 (s, 1 CH_3)		130.4; 130.0; 129.8;
				128.4; 128.2; 127.9
				(aromat. C); 21.7 (CH_3)
		5.08 (dd, H-1)	$J_{1,2}$ = 3.0	75.7 (C-1)
		5.69 (dd, H-2)	$J_{2,3}$ = 10.5	74.5 (C-2)
		6.41 (dd, H-3)	$J_{3,4}$ = 9.5	61.9 (C-3)
		5.44 (dd, H-4)	$J_{4,5}$ = 10.0	78.6 (C-4)
		6.07 (dd, H-5)	$J_{5,6}$ = 3.5	60.9 (C-5)
		5.64 (dd, H-6)	$J_{6,1}$ = 4.0	61.3 (C-6)
		[d]		[d]
(10) [e]	$\varepsilon_{220} \approx 400$	7.55 [D_2O]		
		7.62 (6 C—H); 9.39 (3 N—H)		
		[d]		

[a] Correct elemental analyses were obtained for *(6)*, *(7)* and *(10)*.
[b] In ethanol.
[c] In perdeuterioacetone.
[d] In $CDCl_3$.
[e] IR (Nujol; C_4Cl_6): 3310 (NH), 3140, 3080, 1305, 1250, 1175, 1035, 1010, 984, 855, 826, 804, 750, 730 cm^{-1}; *m/e*: 124; 123 (M^+); 122; 107 ($M^+ - NH_2$); 95 ($M^+ - HCNH$); 81 ($M^+ - C_2H_2NH_2$); 80; 68 ($M^+ - HCN$; $-HCNH$); 67 (100%; $M^+ - 2HCNH$); 61.5 (M^{2+}); 54; 41 ($M^+ - 2C_2H_2NH$); 28 (HCNH).



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[5] Attempts to obtain derivatives of *(10)* by a method analogous to the synthesis of *cis*-monoazatris-σ-homobenzene from azepines and diazomethane [3] have so far failed (*H. Prinzbach, G. Kaupp, R. Fuchs, M. Joyeux, P. Kitzing*, and *J. Markert*, Chem. Ber., in the press).

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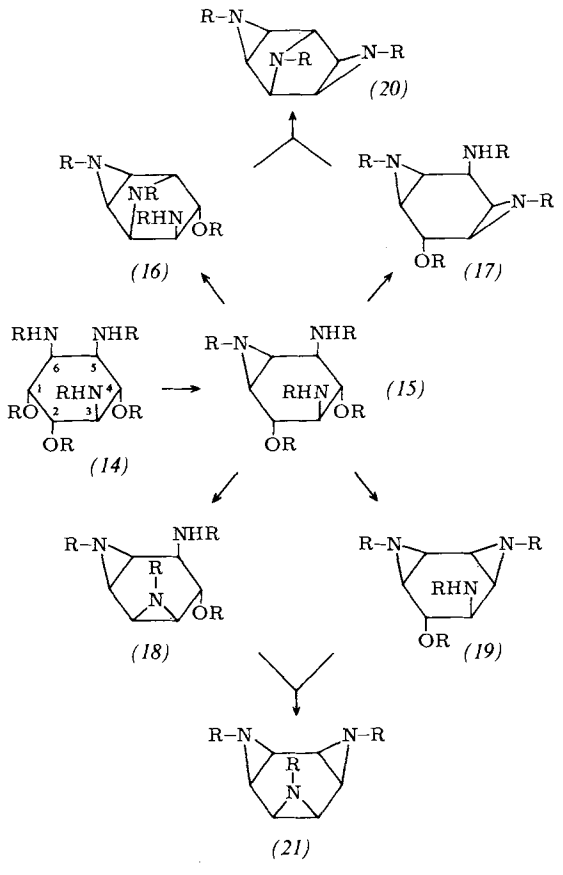
[8] In syntheses involving triamine intermediates of type *(14)* [numbered as *(7)*] corresponding to *(7)*, the first cyclization should preferably involve participation of the *trans*-diaxial substituents on C-1/C-6, yielding *(15)*. However, unlike the situation with *(8)*, the geometric relations



in *(15)* permit four competing partial eliminations, leading to *(16)*—*(19)* and finally to a mixture of *(20)* and *(21)* in proportions that can hardly be estimated in advance. We are in the process of testing this hypothesis experimentally for the case of 3,5,6-tribromo-1,2,4-cyclohexanetriol [9]. That the preparatively accessible, symmetrical 2,4,6-triamino-1,3,5-cyclohexanetriol [1b] [used as tris(hydrogen sulfate)] with the all-equatorial configuration shows little tendency for the formation of aziridines is hardly surprising in view of the extremely unfavorable position of the equilibrium with the all-axial conformer [10].

[9] *L. Knothe* and *H. Prinzbach*, unpublished work.

[10] See *T. Posternak*, Les Cyclitols, Herman, Paris 1962, p. 104.

[11] Piperazine is a good model for the N···N separation in *(10)* (estimated as 2.88 Å). The inductive influence of the nitrogen atom in the β-position on the acidity of the piperazinium monocation can be estimated as 0.9 pK_a unit by comparing the pK_{a1} value (9.83) with the pK_a value (10.73) of the dimethylammonium ion [12]. Starting from $pK_a = 8.0$ [13] for aziridine one thus obtains for *(11)* a pK_a value of $8.0 - 2 \cdot 0.90 = 6.20$. From $pK_{a2} = 5.56$ for the piperazinium dication [12], a value of $pK_a = 6.20 - 4.27 = 1.93$ follows for *(12)*.

[12] Handbook of Chemistry and Physics. 50th edit. 1969—1970, S. D-116.

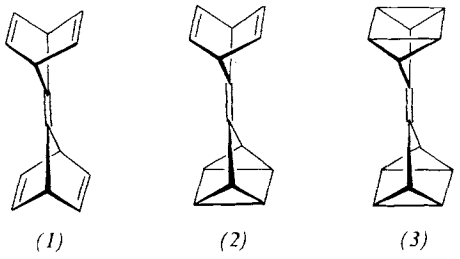
[13] *C. E. O'Rourke, L. B. Clapp*, and *J. O. Edwards*, J. Amer. Chem. Soc. *78*, 2159 (1956).

[14] The structural parameters as determined by X-ray analysis of tris-oxa- *(5)* and trisaza-σ-trishomobenzene *(10)* are essentially comparable (*W. Littke* and *U. Drück*, in preparation).

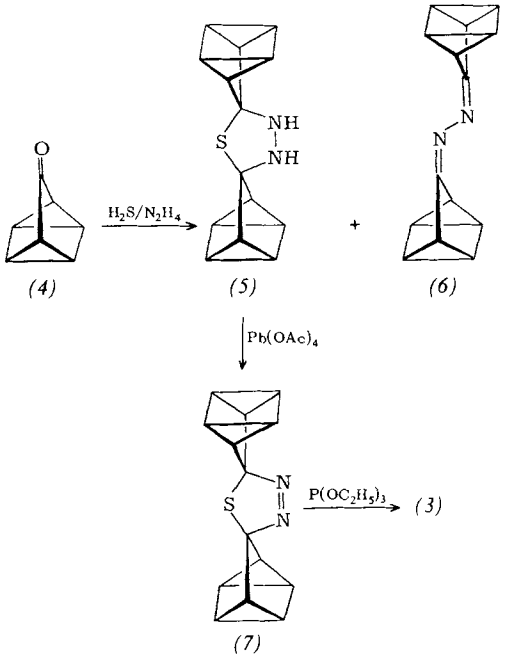
Binorbornadienylidene, Biquadricyclanylidene[1][**]

By *Hubert Sauter, Heinz-Günther Hörster*, and *Horst Prinzbach*[*]

Binorbornadienylidene *(1)*, norbornadienylidenequadricyclane *(2)*, and biquadricyclanylidene *(3)* warrant inter-



est, *inter alia*, as potential intermediates for the synthesis of cyclic cross-conjugated π systems[2,3] and of new polycycles[4].



Starting from quadricyclanone *(4)*[5] we have synthesized *(3)* by the thiadiazolidine method[6,7]. The reaction of H_2S-saturated DMSO solutions of *(4)* with aqueous hydrazine at 0°C leads to about 80% yields of mixtures of *(5)* and *(6)* in a ratio of 6:4. Without separation of the components *(5)* is dehydrogenated to the thiadiazoline *(7)* by lead tetraacetate (CH_2Cl_2; 0°C). After subsequent treatment with triethyl phosphite (80°C), preparative layer chromatography (silica gel, pentane) affords about 20% of *(3)* [based on *(4)*] as colorless readily sublimable prisms.

In the presence of catalytic amounts of palladium(II) chloride norbornadiene complex[8], *(3)* isomerizes in solution

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Table 1. Physical data for compounds *(1)*–*(3)* and *(8)*–*(13)*.

Cpd. m. p. [°C]	UV λ_{max} [nm] (ε)	NMR (τ) [ppm]	
(1)	286 (sh, 120)	3.2	(8H, m),
185	276 (160)	6.2	(4H, m) [a]
	269 (sh, 150)		
	250 (sh, 250)		
	243 (sh, 330) [h]		
(2)		3.0	(4H, m)
		5.9	(2H, m)
		8.0–8.5	(6H, m) [a]
(3)	210 (25000) [b]	8.04	(8H, m)
173		8.10	(4H, m) [c]
(8b)	382 (1200),	2.5 –3.1	(10H, m)
132–133	255 (23000)	3.48	(2H, m)
	230 (18000) [d]	3.71	(2H, s)
		5.71	(2H, m) [e]
(9a)	347 (sh, 3100),	2.76	(10H, m)
191	265 (sh, 12800),	3.02	(2H, m)
	230 (29500) [d]	5.49	(2H, s)
		5.69	(2H, m)
		6.22	(12H, s) [a]
(9b)	330 (4100)	2.6–2.8	(10H, m)
140–141	264 (8900)	2.90	(2H, m)
	233 (21500) [d]	5.48	(2H, s)
		5.67	(2H, m) [a]
(10a)	350 (sh, 2600),	2.70	(10H, m)
204	365 (sh, 12200),	2.97	(2H, m)
	230 (30500) [d]	5.49	(2H, s)
		5.69	(2H, m)
		6.21	(6H, s)
		6.22	(6H, s) [a]
(10b)	332 (4100)	2.6 –2.85	(10H, m)
138	265 (8600)	2.93	(2H, m)
	233 (21000) [d]	5.49	(2H, s)
		5.68	(2H, m) [a]
(11a)	220 (29000) [d]	2.8	(12H, m)
dec. > 100		5.42	(2H, m)
		6.16	(6H, s)
		6.37	(6H, s)
		6.98	(2H, s) [a]
(11b)	220 (22000) [d]	2.8	(12H, m)
191		5.43	(2H, m)
		7.27	(2H, s) [a]
(12a)	248 (sh, ≈18000)	2.7	(10H, m)
dec. > 100	222 (≈20000) [d,f]	6.25	(6H, s)
		6.34	(6H, s)
		6.79	(2H, s)
		7.13	(4H, br.s) [a]
(12b)	233 (sh, 12000),	2.7	(10H, m)
207	220 (21000) [d]	7.03	(2H. s)
		7.26	(4H, m) [a]
(13a)	340 (sh, ≈ 2700)	2.7	(10H, m)
dec. > 150	283 (sh, ≈10000)	5.23	(2H, s)
	240 (≈31000) [d,f]	6.19	(6H, s)
		6.32	(6H, s)
		7.32	(4H, m, AA'BB') [a]
(13b)		4.63	(2H, s)
		7.08	(4H, m) [g]

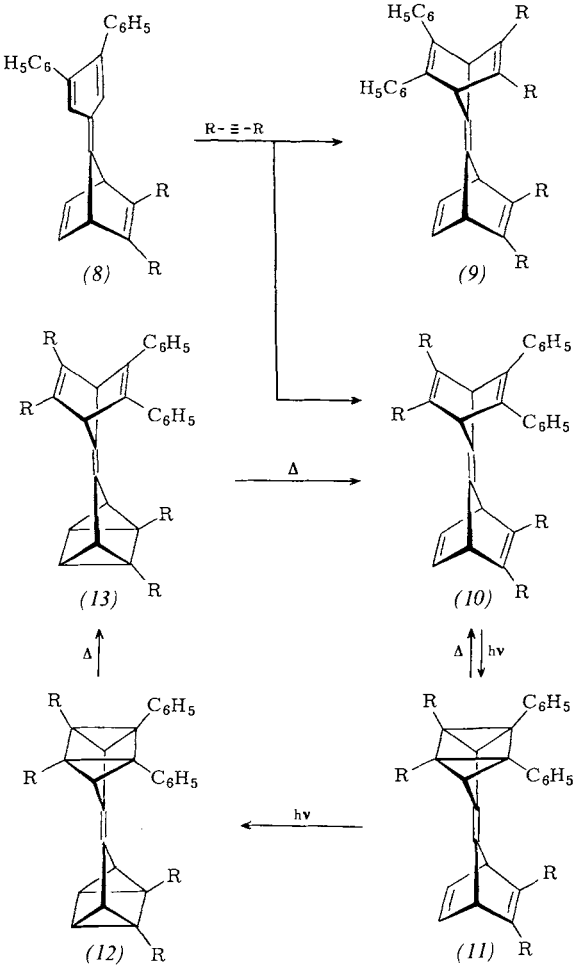
[a] In $CDCl_3$, 60 MHz. [b] In acetonitrile. [c] In CDCl , 220 MHz. [d] In ethanol. [e] In C_6D_6, 60 MHz. [f] Because of low solubility only semiquantitative. [g] In nitrobenzene, 60 MHz. [h] In *n*-hexane.

(CH_2Cl_2) to crystalline binorbornadienylidene *(1)*; ^{1}H-NMR measurements show the conversion to proceed *via (2)*.

(9a), *(9b)*, *(10a)*, *(10b)*, stable derivatives of *(1)*, were obtained by reaction of *(8a)*[3] with dimethyl acetylenedicarboxylate [20°C; *(9a)*:*(10a)* ≈ 1:3 78%] and of *(8b)*[9] with hexafluoro-2-butyne [bomb tube, 20°C; *(9b)*:*(10b)* ≈ 1:1; 90%][10] (isomers separated by preparative layer chromatography).

Direct excitation of *(10a)* with light of wavelength $\lambda > 370$ nm effects selective [2π+2π]cycloaddition in the fourfold substituted norbornadiene partial structure to give *(11a)* (100 mg in 650 ml of CH_2Cl_2; 0 °C; 20 min; Hanovia 450 W Hg high pressure lamp; filter: Pyrex and a 1.4% solution of phenanthrene in CH_2Cl_2). In the case of *(10b)*, irradiation with light of wavelength $\lambda > 280$ nm (150 mg in 300 ml of ether, 0 °C; 2 h; Hanau Q 81 Hg high pressure lamp; pyrex filter) preferentially generates *(11b)* in addition to a little *(12b)*.

Expectedly, *(11a)* is thermally reisomerized readily (60 °C)[11], and *(11b)* less readily (130 °C)[12], to *(10a)* and *(10b)* respectively.



(a), R = CO_2CH_3; *(b)*, R = CF_3

The conversion *(11a)*→*(12a)*, necessarily with light of shorter wavelength ($\lambda > 280$ nm; Hanau Q 81 lamp, Pyrex filter) takes a nonuniform course. *(12a)* can be isolated in 50—60% yield alongside several minor products, some of which are colored. The same result is obtained when *(12a)* is prepared by direct photolysis of *(10a)* (Pyrex filter). Owing to short-wavelength absorption by *(11b)*—direct irradiation (CH_3CN, Vycor filter) leads mainly to polymeric products—*(12b)* is prepared by acetone-sensitized excitation from *(11b)* or directly from *(10b)*.

The ease with which *(12a)* (60 °C) and *(12b)* (130 °C) undergo 2σ→2π cleavage to *(13a)* and *(13b)*, respectively, again differs. At 140 °C *(13a)* affords *(10a)* in about 10% yield.

The structures of all new compounds are confirmed by elemental analysis, by their spectral data (Table 1), and by their mutual interconversions. Assignment of the isomeric pairs *(9a)/(10a)* and *(9b)/(10b)*, and hence the *anti* position of the four R groups in the subsequent products, it is not unequivocal.

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[1] Photochemical Conversions, Part 50.—Part 49: *H. Prinzbach, W. Auge*, and *M. Basbudak*, Chem. Ber. *106*, 1837 (1973).

[2] Cf., *e.g., H. Prinzbach* and *H. J. Herr*, Angew. Chem. *84*, 117 (1972); Angew. Chem. internat. Edit. *11*, 135 (1972).

[3] *H. Prinzbach* and *H. Sauter*, Angew. Chem. *84*, 115 (1972); Angew. Chem. internat. Edit. *11*, 133 (1972).

[4] Compare, *e. g.*, the products of bishomodiene additions to quadricyclanes; *G. Kaupp* and *H. Prinzbach*, Chem. Ber. *104*, 182 (1971).

[5] *R. W. Hoffmann* and *R. Hirsch*, Liebigs Ann. Chem. *727*, 222 (1960).

[6] *D. H. R. Barton, E. H. Smith*, and *B. J. Willis*, Chem. Commun. *1970*, 1226.

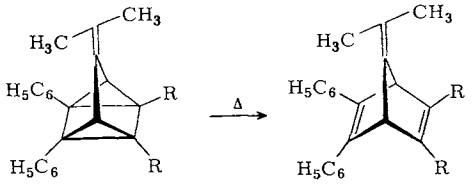
[7] With experimental cooperation from *H. Babsch*.

[8] *E. W. Abel, M. A. Bennett*, and *G. Wilkinson*, J. Chem. Soc. *1959*, 3178.

[9] *H.-G. Hörster*, Diplomarbeit, Universität Freiburg 1972.

[10] This route is superior to that starting from 2,3-diphenylfulvalene[3]; its reaction with the same dienophiles is dominated by dimerization of the hydrocarbon.

[11] The half-reaction time of the model reaction (see below) is 45 min at 64 °C (*H. Sauter*, Dissertation, Universität Freiburg 1973).



[12] Compare the stabilizing action of perfluoroalkyl groups on strained systems, *e. g. M. G. Barlow, J. G. Dingwall*, and *R. N. Haszeldine*, Chem. Commun. *1970*, 1580; *D. M. Lemal* and *L. H. Dunlap, jr.*, J. Amer. Chem. Soc. *94*, 6562 (1972); *R. S. H. Liu* Tetrahedron Lett. *1969*, 1409.

Chemistry of *cis*-Trioxatris-σ-homobenzene. Substitutions by Univalent Nucleophiles[**]

By *Reinhard Schwesinger, Hans Fritz*, and *Horst Prinzbach*[*]

Previous studies of the chemistry of *cis*-trioxatris-σ-homobenzene ("*cis*-benzene trioxide") *(1)* concerned, mainly the $3\sigma \rightarrow 3\pi$ fission to trioxacyclononatriene[1] and the properties as "crown ether"[1a]; preparative applications by substitutions with nucleophiles (Nu) could also be foreseen[1a]. In this connection our interest became directed to the cyclitols *(6)* and/or *(7)* to be expected as a result of three-fold epoxide ring cleavage[2]. We report here typical reactions of *(1)* with univalent N-, S-, O- and C-nucleophiles[3].

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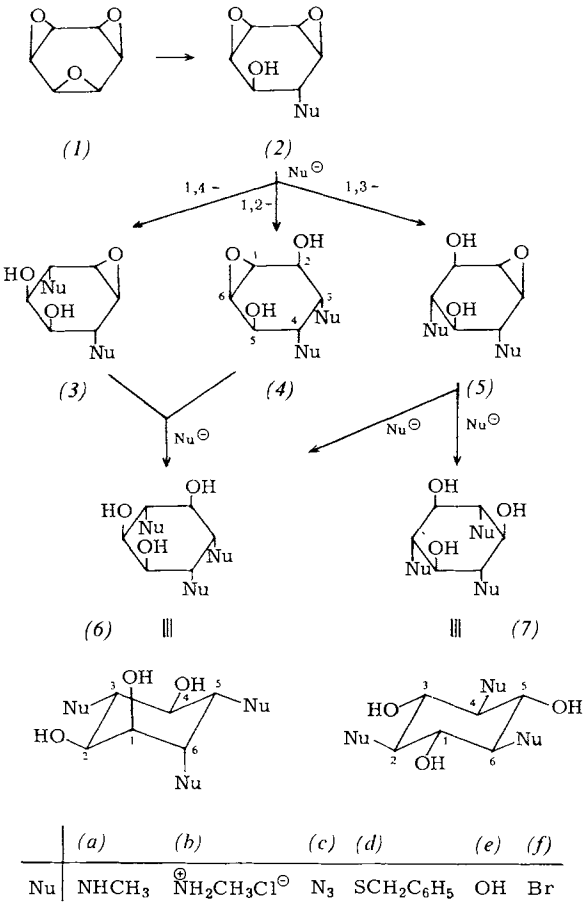
Reaction of *(1)* with an excess of anhydrous methylamine (autoclave, 2h at 20 °C, 1h at 50 °C and 120 °C) affords the 3,5,6-tris(methylamino)-1,2,4-cyclohexanetriol *(6a)*, isolated as the trihydrochloride *(6b)* in 60% yield and liberated by means of an anion exchanger. Proof of the substitution pattern [to be compared with those in *(7a)*] and in particular the e,e,e,e,a,a-conformations of *(6a)* and *(6b)* follow from the numbers and coupling patterns of the ^{1}H-NMR signals obtained for the six ring protons and the methyl protons and also from the ^{13}C-NMR data.



	(a)	(b)	(c)	(d)	(e)	(f)
Nu	$NHCH_3$	$\overset{\oplus}{N}H_2CH_3Cl^{\ominus}$	N_3	$SCH_2C_6H_5$	OH	Br

The behavior of *(1)* with sodium azide is analogous; the triazide *(6c)* is obtained in almost quantitative yield and can be converted into *cis*-triazatris-σ-homobenzene ("*cis*-benzene triimine")[2].

As our first S-nucleophile we used benzyl thiol[4]. With a *ca.* 1.5-fold excess of the thiol (methanol/sodium methoxide, 12 h, 60 °C) we could isolate only 3,5,6-tris(benzylthio)-1,2,4-cyclohexanetriol *(6d)*, which also was proved to have the e,e,e,e,a,a-conformation by the H,H coupling constants. The ^{13}C signals could be assigned to the six cyclohexane carbons atoms by selective heteronuclear decoupling experiments; the resulting order of the chemical shifts of the ^{13}C(OH) nuclei corresponded to those of *chiro*-inositol[5].

Our first hydrolysis experiments with *(1)* were carried out with 2% aqueous perchloric acid. After *ca.* 24 hours' storage at 20 °C and subsequent heating at 70 °C (1 h), NMR control indicated an epoxide-free product, from which crystallization afforded pure inositol in more than 90% yield; on comparison with data in the literature (m. p. IR)[6], this product proved to be *chiro*-inositol *(6e)*.

The fact that the symmetrical substitution pattern *(7)* was not found in any of these substitutions indicates that the

second substitution of *(2)* does not lead to *(5)* but provides substituents Nu at position 4 or 2, giving *(3)* or *(4)*, respectively. However, at least partial reaction by way of *(5)* cannot be excluded, for it must be remembered that acid hydrolysis of, *e.g.*, the epoxide *(5e)* from conduritol B affords mainly *chiro*-inositol *(6e)* by way of the e,e,e,e-conformation and only a little *scyllo*-inositol *(7e)* by way of the a,a,a,a-conformation[7].

To date we have examined two nucleophilic substitutions of *(2)*. The diazide and the dibromide[8] resulting from the 1,2-attack have structures *(4c)* and *(4f)* respectively.

Structure *(4c)* was differentiated from *(3c)* by proton double resonance experiments at 270 MHz which showed that each H—C(OH) proton is flanked by one oxirane and one H—C(N_3) proton. It remains, however, to be clarified to what extent this 1,2-attack on *(2)*, which is undoubtedly surprising on steric grounds, is favored also by other nucleophiles. Since the third substitution step *(4)*→*(6)* is distinctly slower than the steps *(1)*→*(2)* and *(2)*→*(4)*, isolation of the two-fold substituted product *(4)* presents no problem, and there appear to be attractive prospects for synthesis of mixed three-fold substituted 1,2,4-cyclohexanetriols. Correct elemental analyses are available for all the compounds prepared, and ^{1}H- and ^{13}C-NMR spectra for *(4c)*, *(6a)*, *(6b)*, and *(6d)*.

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[1] a) *R. Schwesinger* and *H. Prinzbach*, Angew. Chem. *84*, 990 (1972); Angew. Chem. internat. Edit. *11*, 942 (1972); b) *E. Vogel*, *H.-J. Altenbach*, and *C. D. Sommerfeld*, Angew. Chem. *84*, 986 (1972); Angew. Chem. internat. Edit. *11*, 939 (1972).

[2] *R. Schwesinger* and *H. Prinzbach*, Angew. Chem. *85*, 1107 (1973); Angew. Chem. internat. Edit. *12*, 989 (1973).

[3] Reactions with divalent nucleophiles, see *R. Schwesinger*, *H. Fritz*, and *H. Prinzbach*, Angew. Chem. *85*, 1111 (1973); Angew. Chem. internat. Edit. *12*, 994 (1973).

[4] Further reactions, involving S-nucleophiles such as S_2^{2-} and thioacetic acid and directed to the synthesis of *cis*-trithiatris-σ-homobenzene ("*cis*-benzene trisulfide") are under investigation (*H. Prinzbach*, *S. Kagabu*, and *R. Schwesinger*, unpublished work).

[5] *D. E. Dorman*, *S. Y. Angyal*, and *J. D. Roberts*, J. Amer. Chem. Soc. *92*, 1351 (1970).

[6] *T. Posternak*: Les Cyclitols, Herman, Paris 1962, p. 92.

[7] See [6], p. 178.

[8] Obtained together with 3,5,6-tribromo-1,2,4-cyclohexanetriol by the action of HBr/KBr/H_2O on *(1)*. The monosubstitution product *(2)* (Nu=CF_3CO_2) was also found after reaction of *(1)* with CF_3CO_2H. This product was originally but erroneously considered to be 1,4-dioxocin-6-ol [1a] (*L. Knothe* and *H. Prinzbach*, unpublished work).

Chemistry of *cis*-Trioxatris-σ-homobenzene. Substitutions by Bivalent Nucleophiles[**]

By *Reinhard Schwesinger*, *Hans Fritz*, and *Horst Prinzbach*[*]

According to previous experience, three-fold substitutions of *cis*-trioxatris-σ-homobenzene ("*cis*-benzene trioxide") *(1)* by univalent N-, S- and O-nucleophiles lead preferentially, if not exclusively, to unsymmetrical 3,5,6-substituted 1,2,4-cyclohexanetriols[1]. By using bi- or poly-functional nucleophiles it should be possible to attain other substitution patterns through intramolecular two-fold substitution.

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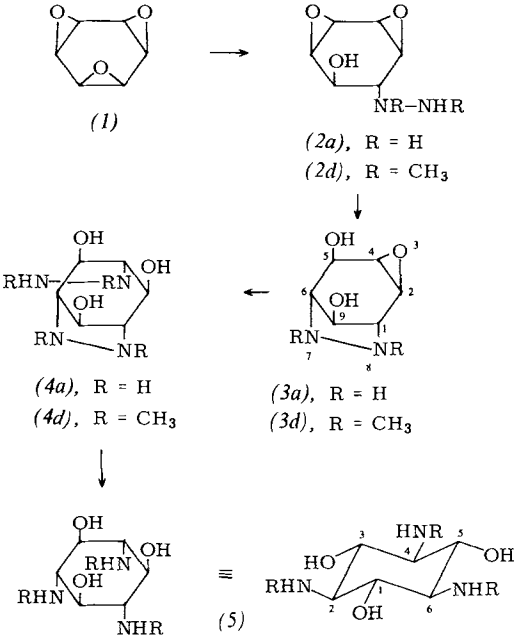
The symmetrical 2,4,6-triamino-substituted cyclitols *(5)*, originally desired for synthesis of *cis*-triazatris-σ-homobenzene[2], can indeed be obtained by treatment of the trioxide *(1)* with hydrazines. For example, reaction of *(1)* with an excess of anhydrous hydrazine and subsequent hydrogenation over Raney nickel, without isolation of the probable intermediates *(2a)*—*(4a)*, afford 2,4,6-triamino-1,3,5-cyclohexanetriol *(5a)* in 85% yield[3]. The all-equatorial arrangement of the six substituents (*scyllo*-inositol structure) follows from the 270 MHz ^{1}H-NMR spectrum, which shows two triplet signals of equal intensity with $J \approx 10$ Hz for the six ring protons. Correspondingly the ^{13}C-NMR spectrum consists of only two signals. The shifts of the H—C(NMR) signals on three-fold protonation to give *(5b)* or acetylation to give *(5c)* are of the usual magnitude. As judged by the selectivity of the reaction *(1a)*→*(5a)*, the reaction, here intramolecular, that follows the stage *(2a)*, clearly occurs preferentially at the 1,3-positions with formation of *(3a)*; *(3a)*, however, can have only the a,a,a,a-conformation that is required for formation of *(4a)* and *(5a)*[3].

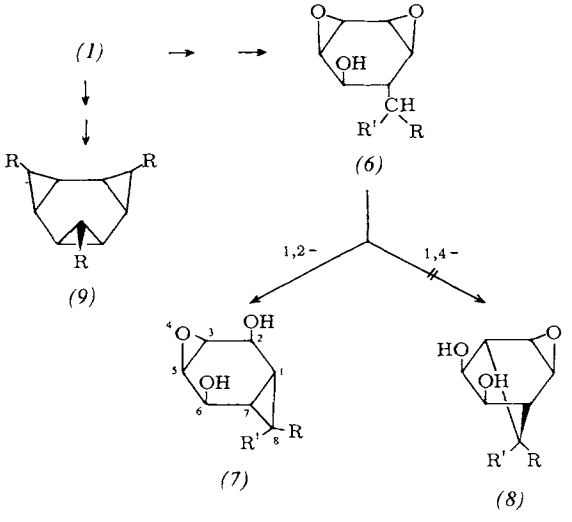
Compounds *(3a)* and thus *(4a)* are experimentally proved to be precursors of *(5a)* by the results of the reaction with *N*,*N'*-dimethylhydrazine. A crystalline 1:1 adduct is obtained (although so far only in the moderate yields of 20—30%) for which ^{1}H-NMR spectra indicate structure *(3d)* with good certainty. We are studying compounds of types *(3)* and *(4)* with a view to using them for preparation of streptamine or similar products[4].



(5)	(a)	(b)	(c)	(d)
R	H	$H_2^{\oplus}$	$COCH_3$	CH_3

Analogously to "*cis*-benzene triamine"[2], carbocyclic *cis*-tris-σ-homobenzene compounds *(9)* should be accessible from *(1)* by three-fold "reversal" of the epoxide ring by means of C-nucleophiles. Because of the known ready σ→π cleavage of *(9)* we sought derivatives containing π-acceptor groups, whose stabilizing effect on the σ-structures has been repeatedly demonstrated[5]. *(1)* (1.2 mol) reacts quantitatively with methyl cyanoacetate (catalytic

amounts of sodium methoxide, 24 h, 20 °C). However, according to its ^{1}H- and ^{13}C-NMR spectra the product, of composition $C_{10}H_{11}NO_5$, is not *(6a)* but methyl 8-cyano-2,6-dihydroxy-4-oxatricyclo[5.1.0.0^{3,5}]octane-8-carboxylate *(7a)*. This arises by intramolecular substitution at the 1,2-positions of the carbanion formed from *(6a)*. The ^{1}H- and ^{13}C-NMR data cannot be brought into accord with the alternative *(8a)* resulting from 1,4-substitution of *(6a)* and also characterized by a symmetry plane; *inter alia*, the occurrence of a cyclopropane ring is proved by the signals of protons 1-H, 7-H ($\tau = 7.95$) and their large ^{13}C—H coupling (> 150 Hz). The stereochemistry at C-8 is uncertain, although *endo*-arrangement of the cyano group is probable. The neighboring group effect in *(6a)*, which is unfavorable for formation of *(9)* and has often been observed in inositol and sugar chemistry[6], also determines the result of reaction with maleodinitrile in methanol: This affords the analogous imidic ester *(7b)* in *ca.* 70% yield, and *(7b)* is converted into the cyano ester *(7a)* when heated in very dilute acetic acid.



(a), R = CO_2CH_3, R' = CN
(b), R = $C(OCH_3)$=NH, R' = CN

We are currently investigating to what extent univalent [*e. g.* CN^-, $C(CO_2R)_3^-$] and α,γ-bivalent carbanions [*e. g.* from $CO(CH_2CO_2R)_2$, $P(CH_2CO_2R)_3$] can be applied for synthesis of, respectively, unbridged[7] and bridged[8] derivatives of *(9)*[9].

Correct elemental analyses are available for all the new compounds except *(5b)*, also ^{1}H-NMR spectra for *(3d)*, *(5b)* and *(7b)*, and both ^{1}H- and ^{13}C-NMR spectra for *(5a)*, *(5c)* and *(7a)*.

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[1] *R. Schwesinger, H. Fritz,* and *H. Prinzbach*, Angew. Chem. *85*, 1110 (1973); Angew. Chem. internat. Edit. *12*, 994 (1973).

[2] *R. Schwesinger* and *H. Prinzbach*, Angew. Chem. *85*, 1107 (1973); Angew. Chem. internat. Edit. *12*, 989 (1973).

[3] *T. Posternak:* Les Cyclitols. Herman, Paris 1962, p. 96. The tri-*N*-acetate *(5c)* was obtained from *myo*-inositol in a total yield of 0.1% in a 15-step synthesis by way of the hexaacetate; it was characterized as monohydrate: *S. Ogawa, T. Abe, H. Sano, K. Kotera,* and *T. Suami*, Bull. Chem. Soc. Jap. *40*, 2405 (1967). The symmetricall all-*cis*-isomeric triaminocyclohexanetriol is accessible by hydrogenation of the triaminophloroglucinol: *G. Quadbeck* and *E. Böhm*, Chem. Ber. *89*, 1645 (1956); *F. W. Lichtenthaler* and *H. Leinert, ibid. 99*, 903 (1966). We thank Prof. *T. Posternak*, Geneva, for a reference sample of *scyllo*-inositol.

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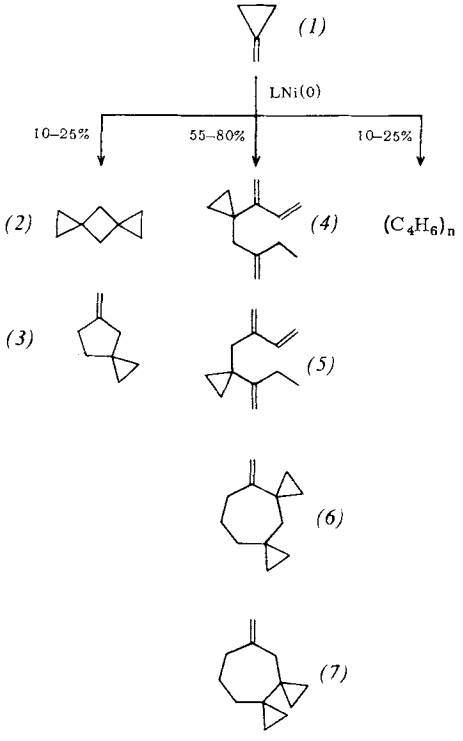
Trimerization of Methylenecyclopropane on Triorganophosphane-Modified Nickel(0) Catalysts

By *Paul Binger* and *John McMeeking*[*]

In Memory of Karl Ziegler

Methylenecyclopropane *(1)* can be converted into the cyclodimers *(2)* and *(3)* on nickel(0) catalysts[1] and particularly well on such catalysts if modified by fumaric or maleic esters[2]. We have now found that, on triorganophosphane-modified nickel(0) compounds, *(1)* affords trimer mixtures in up to 80% total yield. The mixture consists mainly of the trienes *(4)* and *(5)*, together with the dispiromonoenes *(6)* and *(7)* containing a seven-membered ring. These products are always accompanied by 10—25% of dimers and undistillable higher oligomers (see Table 1).



The trimers *(4)*—*(6)* are very probably formed *via* the same intermediates as the dimers *(2)* and *(3)*[1], with subsequent addition of a Ni—C linkage to the C=C bond of *(1)*.

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The catalysts are prepared from $Ni(COD)_2$[3] and phosphane in the molar ratio 1:1. *Ca.* 1 mol of *(1)* can be converted by 1 mmol of the Ni catalyst. Apparently the C—C bond formation occurs on a LNi(0) species, since an excess of the phosphane does not influence the course of reaction. Accordingly, *(1)* is oligomerized only slowly, incompletely, and less specifically on $L_2Ni(0)$ compounds (L_2 = tetraphenyl- or tetracyclohexyl-ethylenebisphosphane) even at 50—60 °C. Triaryl phosphite-Ni(0) complexes are catalytically inactive towards *(1)* under comparable conditions; they probably form stable ligand-nickel(0)-olefin complexes in a stoichiometric reaction[4].

Table 1. Oligomerization [a] of methylenecyclopropane *(1)* on phosphane-modified nickel(0) catalysts prepared from equimolar amounts of $Ni(COD)_2$ and a phosphane PR_3.

PR_3	Dimers (C_8H_{12}) [b] yield [%]	*(2)* : *(3)* : rest [d]	Trimers ($C_{12}H_{18}$) [b] yield [%]	*(4)*	*(5)* : *(6)* : *(7)* : rest [d]	Higher oligomers [c] yield [%]
$P(iC_3H_7)_3$	17	13 : 80 : 7	69	32	: 46 : 16 : 2 : 4	14
$P(C_6H_{11})_3$	19	17 : 70 : 13	54	32	: 40 : 16 : 7 : 5	27
$P(iC_3H_7)_2tC_4H_9$	12	6 : 79 : 15	79	8 / 11 [e]	: 8 : 60 : 9 : 4	9
$P(tC_4H_9)_3$	24	47 : 10 : 43 [f]	5	0	: 0 : 80 : 0 : 19	71
$P(C_6H_5)_3$	12	10 : 74 : 16	42	44	: 45 : <1 : 5 : 5	46

[a] At 25—60 °C with >90% conversion of *(1)*.
[b] The isomer proportions were determined by gas chromatography.
[c] Undistillable in a high vacuum.
[d] Numerous hydrocarbons each <1%.
[e] As well as *(4)* an unidentified compound appeared with almost the same retention time [6].
[f] Contain 15% of a compound with the same retention time as dispiro[2.0.2.2]octane [5].

The influence of the phosphane substituents on the course of the reaction and the composition of the products is shown in Table 1. The structures of the new $C_{12}H_{18}$ compounds were determined by means of their IR, MS, and particularly their ^{1}H-NMR spectra.

Trimerization of methylenecyclopropane (1)

(1) (40 g, 0.74 mol) was added dropwise to a yellow catalyst solution, prepared from $Ni(COD)_2$ (0.57 g, 2.1 mmol) and *tert*-butyldiisopropylphosphane (0.5 g, 2.7 mmol) in benzene (20 ml) over 2 h at room temperature. The red solution rapidly warmed to 50 °C (max.; occasional water-bath cooling). Reaction was complete after 6 h at 30—50 °C. Subsequent distillation gave, besides a residue (3.3 g), a colorless distillate (51.8 g) of b.p. 0—52 °C/0.5 torr, shown by gas chromatography to have the composition: *(1)* 1.6%, benzene 36.7%, *(2)* 0.4%, *(3)* 5.4%, 1,4-COD 1.4%, 1,5-COD 0.9%, *(4)* and unidentified compound[6] 4.2% and 5.8%, *(5)* 4.3%, *(6)* 30.1%, *(7)* 4.9%, rest 4.3%, 11 peaks <1%. Fractional distillation through a 1.5-m spinning-band column afforded *(6)* (10.3 g: 74.8% pure by gas chromatography) of b.p. 88—92 °C/12 torr, which contained 13.6% of *(7)* as impurity; the rest was shown by gas chromatography to contain *(4)* 1.2%, unidentified compound[6] 2.2%, *(5)* 3.5%, inidentified compound 2.4%, and a residue 1.9%, *ca.* 8 peaks <1%.

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[6] Note added in proof (Oct. 1, 1973): This compound has meanwhile been identified as 1-[(1-methylcyclopropyl)methyl]-1-(1,3-butadien-2-yl)cyclopropane.

Preparation of 4,6-Dioxa-1-azabicyclo[3.3.0]-octanes from Iminodiethanols and Nitriles

By *Klaus Burzin* and *Roland Feinauer*[*]

Dedicated to Professor Heinrich Hellmann on the occasion of his 60th birthday

Alkyl-substituted bicyclic amide acetals of type *(3)* (R^1 or R^3 = H) have only recently become available, namely by cycloaddition of epoxides to Δ^2-1,3-oxazolines[1-3].

The amide acetals *(3)* studied so far (R^1 or R^3 = H) have proved very reactive compounds by whose reactions with carboxylic acids, phenols, amines, aldehydes and alkylating agents numerous new classes of compounds have become accessible[3].

Within the framework of studies of the preparation of Δ^2-1,3-oxazolines from amino alcohols and nitriles[4] we have now found a simpler route for synthesis of alkyl-substituted 4,6-dioxa-1-azabicyclo[3.3.0]octanes *(3)*, namely by treatment of iminodiethanols *(1)* with aliphatic nitriles *(2)* in the presence of catalytic amounts of the sodium alcoholate derived from the iminodiethanol reactant. In this way the trisubstituted derivatives *(3i)*—*(3l)* also become available in a single-stage process that avoids the need for preparation (often experimentally difficult) of Δ^2-1,3-oxazolines from the cheap components *(1)* and *(2)*.

The structures of the compounds *(3)* are proved by IR, ^{1}H-NMR and ^{13}C-NMR spectra as well as by elemental analyses. For *(3a)*, *(3b)*, *(3e)* and *(3f)* it was shown that their physical properties accord with those of material prepared by other routes[1].

From the NMR spectra it is clear that the compounds *(3e)*—*(3l)* are diastereoisomeric mixtures; their separation has not yet been attempted.

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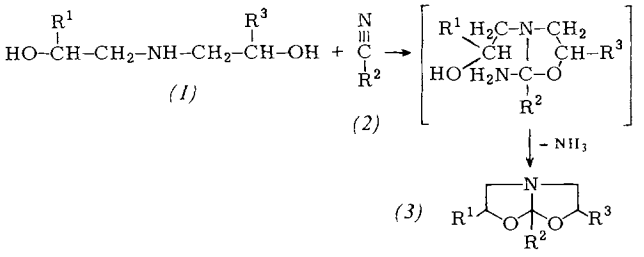

(1) (2) (3)

(3)	R^1	R^2	R^3	Yield [%] [a]	Method	B.p. [°C/torr]	n_D^{20}
a	H	CH_3	H	33	A	75/22	1.4562
b	H	C_2H_5	H	41	A	81—83/22	1.4569
c	H	C_3H_7	H	31	B	106/25	1.4450
d	H	C_4H_9	H	44	B	114/24	1.4448
e	H	CH_3	CH_3	42	A	86/24	1.4471
f	H	C_2H_5	CH_3	52	A	93/24	1.4492
g	H	C_3H_7	CH_3	36	B	109/19	1.4504
h	H	C_4H_9	CH_3	38	B	124/24	1.4520
i	CH_3	CH_3	CH_3	37	A	86/19	1.4402
j	CH_3	C_2H_5	CH_3	33	A	93/24	1.4492
k	CH_3	C_3H_7	CH_3	39	B	114/24	1.4448
l	CH_3	C_4H_9	CH_3	26	B	127/24	1.4472

[a] Based on the nitrile used. Yields were not optimized; conversions amounted to more than 95%.

4,6-Dioxa-1-azabicyclo[3.3.0]octanes (3)

(1) (1.0—1.1 mol, in which 1 mol-% of sodium has been previously dissolved) and *(2)* are heated together at 140 °C under reflux in an atmosphere of inert gas for 20 (A) or 40 h (B); ammonia is evolved. After the reaction distillation is carried out under dry nitrogen since all the products *(3)* are bases that attract water and carbon dioxide.

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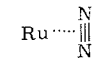
π-Bonded Nitrogen in a Crystalline Nickel-Lithium Complex

By *Klaus Jonas*[*]

In Memory of Karl Ziegler

A few years ago we reported on the first dinitrogen-nickel(0) complex $[(C_6H_{11})_3P]_2NiN_2Ni[P(C_6H_{11})_3]_2$[1] in which two nickel atoms are bonded end-on to the two nitrogen atoms[2]. This kind of bonding (M–N≡N or M–N≡N–M) has been foun in all dinitrogen transition metal complexes so far discovered and subjected to X-ray analysis. Such bonding is also in accord with theoretical considerations and calculations[3] which predict complexes having π-bonded (edge-on) N_2 to be less stable than those with end-on bonded nitrogen.

In 1970 *Armor* and *Taube* first reported π-bonded dinitrogen in a ruthenium complex[4]: they postulated the occurrence of

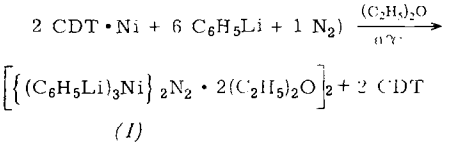


as transition state in the intramolecular $^{14}N—^{15}N$ exchange

$[(H_3N)_5Ru\cdot{}^{14}N^{15}N]^{2+} \rightleftharpoons [(H_3N)_5Ru\cdot{}^{15}N^{14}N]^{2+}$.

Evidence constituting a direct proof of π-bonded dinitrogen, albeit at very low temperature (10 K), has recently been obtained by *Ozin* and *Vander Voet*[5] from IR studies in a cobalt matrix. The present communication describes a crystalline nickel-lithium complex having molecular nitrogen unequivocally π-bonded to the transition metal which is stable at room temperature.

Studies on the action of nickel(0) complexes on organometallic compounds of Group IB to IIIB elements[6] have revealed, *inter alia*, that reaction of all-*trans*-1,5,9-cyclododecatrienenickel(0)[7] with phenyllithium in the presence of molecular nitrogen leads to a complex *(1)* which is stable at room temperature:



(1)

Volumetric determinations show that 1 N_2/2 Ni is consumed during formation of complex *(1)*. Its stoichiometric composition follows from the Ni content and from the reaction of *(1)* with ethanol, during which Ni is precipitated quantitatively as the metal. The filtrate is shown by GC to contain a quantity of diethyl ether corresponding to formula *(1)* and an alkalinity determination reveals $3\,C_6H_5Li$/Ni.

The nitrogen *(1)* can be partly or completely displaced by 1,5-cyclooctadiene or $(C_6H_5)_2P(CH_2)_2P(C_6H_5)_2$/$B(C_6H_5)_3$ [$LiB(C_6H_5)_4$ only being formed in 30% yield]. The reaction of *(1)* with ethylene is particularly characteristic since the nitrogen is then liberated quantitatively.

Apart from the characteristic frequencies of the phenyl groups and ether, the IR spectrum of complex *(1)* contains no other bands that can be assigned to vibrations of the N_2 system. Possibly the NN vibration, if it is at all IR active, may be shifted to such long wavelengths (<1550 cm^{-1}) that it is obscured by other bands.

X-ray analysis[8] shows *(1)* to be dimeric ($n=2$) and the complex to contain Ni—Ni bonds to which the two π-bonded N_2 molecules are oriented at right angles. The N—N bond is extremely long (1.35 Å). This may be

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due to a cooperative effect since N_2—Ni_2 π-bonding seems to be accompanied by an interaction between the lithium atoms and the end-on positions of the nitrogen. A cooperative effect of this kind, *i.e.* a joint action of several metal atoms (Fe and Mo) on N_2, is also suspected in enzymatic nitrogen fixation.

The ability of ethylene to smoothly displace the clearly strongly activated (N—N: 1.35 Å) nitrogen is truly remarkable. This reaction presumably also involves liberation of phenyllithium as well as N_2 to form a novel bimetal-olefin complex *(2)*, which can be prepared independently from phenyllithium, CDT·Ni, and ethylene.

$$2\ C_6H_5Li + CDT \cdot Ni + C_2H_4 \xrightarrow{(C_2H_5)_2O}$$

$$(C_6H_5Li)_2NiC_2H_4 \cdot (C_2H_5)_2O + CDT$$

(2)

The ^{1}H-NMR spectrum of *(2)* in [D_8]tetrahydrofuran shows a singlet at $\tau = 9.87$ for the ethylene protons. The extremely pronounced shielding of the protons attached to the complexed double bond compared to that in phosphane-olefin- and pure olefin-nickel(0) complexes, suggests an enhanced electron density on ethylene in *(2)*. This probably also applies to the dinitrogen complex *(1)* and is manifested in the extreme elongation of the N—N bond.

The systems CH_3Li/CDT·Ni and C_6H_5Li/C_6H_5Na/CDT·Ni also bind molecular nitrogen in the ratio $Ni:N_2 = 2:1$. Studies are in progress to establish whether the nitrogen in the above systems can be induced to react stoichiometrically or even catalytically.

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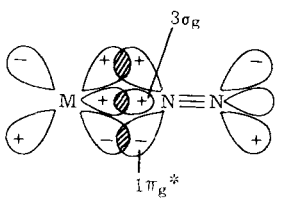
Molecular Structure of a π-Dinitrogen-Nickel-Lithium Complex

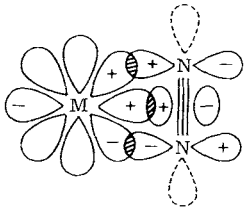
By *Carl Krüger* and *Yi-Hung Tsay*[*]

In Memory of Karl Ziegler

Structural analyses of dinitrogen complexes of numerous transition metals[1] have so far always indicated a linear M—N≡N arrangement *(1)*. We recently reported the structure of such a system having nickel as central atom[2]. The fixation of the N_2 ligand in compounds of this type is accomplished by a σ bond between the $3\sigma_g$ orbital of the nitrogen and hybrid orbitals of the metal and by back bonding from the metal to the vacant $1\pi_g^*$ orbital of the nitrogen (see *(1)*)[3].



(1)



(2)

A bonding involvement of the nitrogen lone pair should permit formation of olefin-like π complexes[4] such as are assumed in the reaction sequence of natural nitrogen fixation. X-ray structure analysis of the novel complex $[(C_6H_5Li)_6Ni_2N_2\{(C_2H_5)_2O\}_2]_2$[5] shows that the N_2 ligand does indeed possess an arrangement like that in *(2)*.

The complex forms dark red crystals from diethyl ether (unit cell: $a = 14.591(3)$, $b = 25.503(3)$, $c = 14.126(4)$ Å; $\beta = 113.32(2)°$; $P2_1/a$; $Z = 2$). The heavy atom skeleton was determined by direct methods from 4915 measured uncorrected structure amplitudes ($I_0 > 2\sigma(I_0)$; $\lambda = 1.5418$)[6], and the arrangement of the rest of the molecule could be deduced from repeated Fourier syntheses. Anisotropic refinement has so far led to an *R* value of 9.3. The geometry of the centrosymmetric dimeric molecule is shown in Figure 1; Figure 2 depicts the internal skeleton of the strongly polar complex (Ni, N, and Li atoms).

A considerably elongated Ni—Ni linkage (2.687 Å)[7] is bridged by a nitrogen molecule almost at right angles with respect to the N—N bond. The two independent Ni atoms display a strongly distorted trigonal pyramidal geometry. The trigonal planes contain two phenyl carbon atoms and the N_2 molecule and the apices are occupied by a Ni atom and a Li atom.

The two nitrogen molecules are linked *via* two Li atoms to form a centrosymmetric six-membered ring $(—Li6—N1—N2—)_2$ (see Fig. 2), and the two halves of the molecules are additionally linked *via* a bridge Li2—A—Li5. Whereas the N2 atom is bonded end-on to a Li atom (Li1), the N1 atom is bonded to three Li atoms (Li3, Li5, Li6) to form a tetrahedron. This grouping can be derived from the skeleton of $[LiCH_3]_4$[8] and analogous compounds[9] by replacing one Li atom by nitrogen and assuming the formation of a two-electron four-center bond between N1 and Li3—Li5—Li6. The Li—Li distances found correspond to those in $[LiCH_3]_4$. A further coordination site of this system is occupied by a phenyl ring (Fig. 1, B), leading approximately to a trigonal-bipyramid with Li3—Li5—Li6 as base. Li3 and Li4 additionally bridge the Ni—Ni bond, whereas Li2 and Li4 are only bonded to one Ni atom each. The compound contains two σ-bonded phenyl groups per nickel atom (C, D, E, F; Ni—C: 1.96 Å, C—Ni—C: 102 and 104°), C and D undergoing additional bonding *via* Li4 (I). The phenyl rings A and B are not bonded to nickel but only to lithium.

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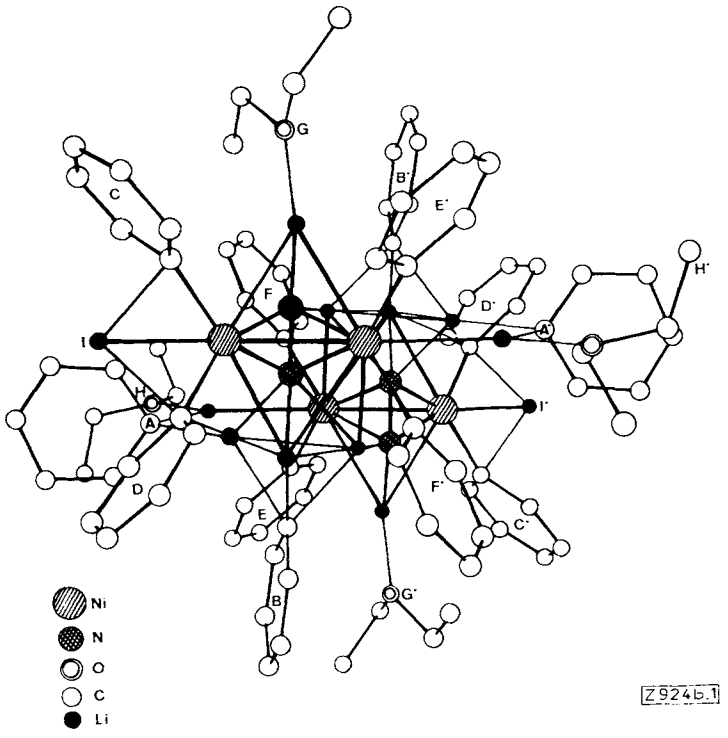

Fig. 1. Molecular structure of the complex $[(C_6H_5Li)_6Ni_2N_2\{(C_2H_5)_2O\}_2]_2$.

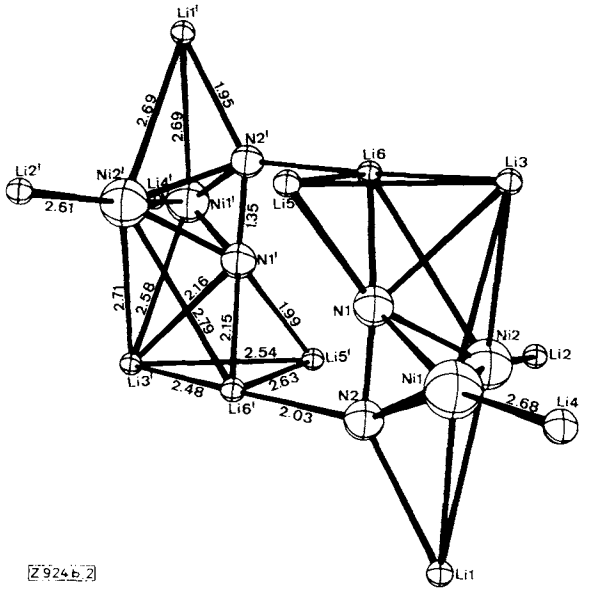

Fig. 2. Internal skeleton of the complex $[(C_6H_5Li)_6Ni_2N_2\{(C_2H_5)_2O\}_2]_2$.

Vacant coordination sites on Li1 and Li2 are occupied by ether molecules (G, H); an analogous, but only partial ($\approx 30\%$), occupation of the coordination site on Li4 (not shown in Fig. 1) hinders further refinement.

On complex formation the N—N bond undergoes extreme elongation to 1.35 Å (1.097 Å in free N_2 and similar values in end-on N_2 complexes[1, 2]). This elongation and also the very fact that π bonding to nickel is possible at all (Ni1—N1: 1.92 Å; Ni1—N2: 1.91 Å; Ni2—N1: 1.93 Å; Ni2—N2: 1.94 Å) are attributable primarily to the electron acceptor properties of the lithium (Li1 and Li3, Li5, Li6 respectively) which enhance the back bonding from the nickel to the nitrogen.

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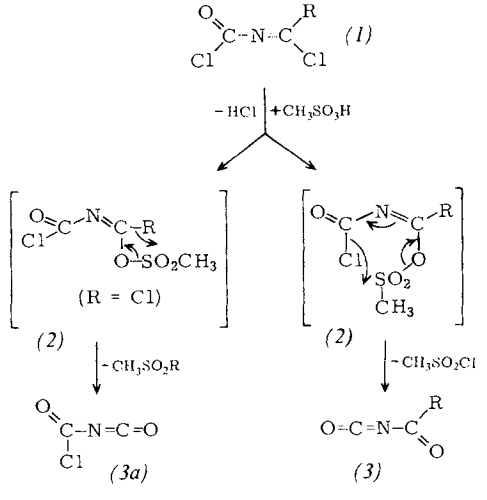
Acyl Isocyanates from *N*-(Chlorocarbonyl)imidoyl Chlorides

By *Hermann Hagemann*[*]

Acyl isocyanates *(3)* are extremely reactive compounds which, unlike the sulfonyl isocyanates of comparable reactivity, cannot be prepared by phosgenation of the corresponding amides. By the following considerations and experiments it has been found that they can be obtained by partial hydrolysis of the readily accessible imidoyl chlorides *(1)*[1–3].



Isocyanide dichlorides can, in general, be converted into isocyanates by, *e.g.*, methanesulfonic acid with replacement of both chlorine atoms by an oxygen atom[4]. However, *N*-chlorocarbonyl isocyanate *(3a)* would be obtained from chlorocarbonyl isocyanide dichloride even if only one chlorine atom of the isocyanide dichloride group were replaced whilst the second chlorine atom to be exchanged was that of the chlorocarbonyl group. 1,4- in place of

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1,2-elimination of methanesulfonyl chloride from the hypothetical intermediate *(2)* would have to occur. That such a reaction can occur has been shown by conversion of the *N*-(chlorocarbonyl)imidoyl chlorides *(1b)*—*(1d)* (R ≠ Cl)[1-3] into the acyl isocyanates *(3b)*—*(3d)* (Table 1)[5].

Table 1. Acyl isocyanates *(3)* obtained from *N*-(chlorocarbonyl)imidoyl chlorides *(1)*.

	R	B.p. [°C/torr]	Yield [%]	Ref.
a	Cl	64/760	88	[4c, 6]
b	phenylthio	120/14	92	[7]
c	*p-tert*-butylphenoxy	140/13	75	
d	phenyl	90/12	90	[8]

N-Chlorocarbonyl isocyanate (3a)

Methanesulfonic acid (924 g, 9.53 mol) is added dropwise to a solution of *(1a)*[3,9] (1530 g, 9.53 mol) in toluene (600 ml) at *ca.* 30 °C. When evolution of hydrogen chloride ceases the mixture is heated to a bath temperature of 125 °C and the chlorocarbonylcarbamidoyl chloride (ClCONHCOCl) that crystallizes in the condenser is continuously returned to the flask by means of hot toluene (*ca.* 230 ml). Pure *(3a)* is then distilled off through a column. As soon as the boiling point rises, the column is shut off and evolution of hydrogen chloride resumed through a reflux condenser. 887 g of *(3a)* are obtained.

N-(Phenylthio)carbonyl isocyanate (3b)

Methanesulfonic acid (54.8 g, 0.57 mol) is added dropwise over *ca.* 1 h to *(1b)* (133.5 g, 0.57 mol) at 50 °C. Vigorous evolution of HCl sets in and is complete after 2 h at 100 °C. 94 g of *(3b)* are obtained by distillative separation from methanesulfonyl chloride.

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Bis(amido)sulfur Tetrafluorides[**]

By *Rainer Höfer* and *Oskar Glemser*[*]

Addition of sulfur tetrafluoride to the SN triple bond of the difluoronitridosulfur amides $N{\equiv}SF_2{-}NSF_2$ *(1)* and $N{\equiv}SF_2{-}NSOF_2$ *(4)* affords the disubstituted derivatives of sulfur hexafluoride $F_2SN{-}SF_4{-}NSF_2$ *(2)* and $F_2SN{-}SF_4{-}NSOF_2$ *(5)*, which exist in the reaction mixture as *cis-trans*-isomers.

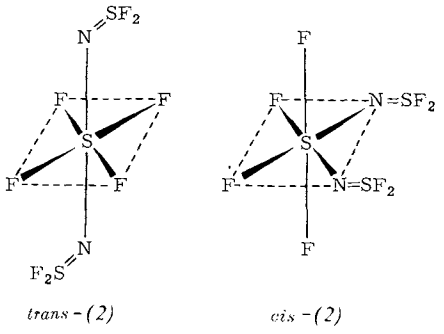

Fig. 1. Structure of the *cis-trans*-isomers of bis(*N*-difluorosulfuramido)sulfur tetrafluoride *(2)*.

In this way bis(*N*-difluorosulfuramido)sulfur tetrafluoride *(2)* is obtained by treating SF_4 with *N*-(difluoronitridosulfur)sulfur imide difluoride[1] *(1)* as follows:

$$N{\equiv}SF_2{-}NSF_2 + SF_4 \xrightarrow[CsF]{80\,^\circ C} F_5S{-}N{=}SF_4{-}N{=}SF_5$$

(1) *(2)*

or with bis(*N*-trimethylsilylimido)sulfur difluoride[2] *(3)* as follows:

$$(CH_3)_3Si{-}N{=}SF_2{=}N{-}Si(CH_3)_3 + 2\,SF_4$$

(3)

$$\xrightarrow[CsF]{100\,^\circ C} \textit{(2)} + 2\,(CH_3)_3SiF$$

(2) is a water-clear liquid that polymerizes within a few days to a viscous, dark brown product but can be kept for a longer time in quartz vessels cooled in Dry Ice. Both the compound itself and the polymer are extremely sensitive to hydrolysis; reaction with water leads to explosive decomposition. The composition of *(2)* is proved by complete elemental analysis, and the structure by NMR and IR spectra.

IR (cm^{-1}): 1260 vs (νS=N); 835 vs, 805 vs, 736 vs, 684 s, (ν_sSF, ν_{as}SF); 655 m, 584 s, 578 s, 480 m, 470 sh, 438 w, 392 m. ^{19}F-NMR (ext. $CFCl_3$): Evaluation of the spectrum is made difficult by the existence of a mixture of geometrical isomers (*cis*:*trans* = 25:75). *trans-(2)* gives a spectrum of the 1st order: $\delta SF_4 = -111.06$ (quintet), $\delta NSF_2 = -55.73$ ppm (quintet); $^4J_{FF} = 14.7$, *cis-(2)* gives a spectrum of higher order of the type $A_2BBX_2X'_2$, whose analysis is not yet complete[3], provisional data being: $\delta SF_e(BB')$ and $\delta SF_a(A) = -100$ to -105, δNSF_2 (XX') $= -54.0$ ppm; J_{AB}, $J_{AB'}$, $J_{BB'} \approx 150$, J_{AX}, $J_{AX'}$, J_{BX}, $J_{B'X'} = 12$ to 14, $J_{B'X}$, $J_{BX'} \approx 1$ Hz.

Mass spectrum: *m/e* (rel. intensities) = 276 M^+ (0), 257 $(M-F)^+$ (13), 238 $(M-F_2)^+$ (1), 219 $(M-F_3)^+$ (1), 200 $(M-F_4)^+$ (0.5), 168 $(NSF_2)_2^+$ (1), 154 $SF_2NSF_2^+$ (15), 135 $SFNSF_2^+$ (3), 108 SF_4^+ (3), 89 SF_3^+ (100), 84 NSF_2^+ (90), 70 SF_2^+ (100), 65 NSF^+ (38), 51 SF^+ (40), 46 NS^+ (100). Mol.-wt.: calc. 276.1, found 274, 276 (Regnault).

The bis(amido)sulfur tetrafluoride *(5)*, which is differently substituted on N and N', is formed on reaction of SF_4

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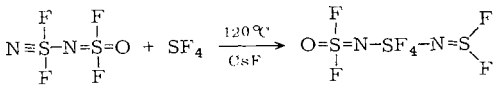
with *N*-(difluoronitridosulfur)sulfur imide oxide difluoride[4] *(4)*, analogously to the first of the above syntheses of *(2)*, thus:



(4) *(5)*

(5) is a colorless liquid, which is appreciably more stable than *(2)* since it can be kept without decomposition for days in glass vessels. Its composition, also, is proved by elemental analyses and its structure by IR and NMR spectra.

IR (cm^{-1}): 1420 vs ($\nu_{as}NSO$); 1296 s ($\nu S{=}N$); 1240 vs ($\nu_s NSO$); 860 vs br, 820 sh, 765 vs, 732 s, 685 s (ν_s, $\nu_{as}SF$); 580 s, 570 s, 490 vw, 468 vw, 457 w, 393 vw) (deformation vibrations). ^{19}F-NMR (ext. $CFCl_3$): for *trans-(5)* the spectrum of the 1st order corresponds to the type $A_4K_2X_2$. The NSF_2 group is readily identified in the general spectrum; the signal of the $NS(O)F_2$ group, however, overlaps the signals of the *cis*-isomer: $\delta NS(O)F_2(K) = -45.6$, $\delta NSF_2(X) = -53.5$, $\delta SF_4(A) = -112.0$ ppm; $J_{AK} = 14.3$, $J_{AX} = 10.5$, $J_{KX} < 0.5$ Hz. Provisional data for *cis-(5)* ($A_2BCK_2X_2$) are: $\delta SF_a(A) = -102$ to -105, $\delta SF_e(B)$ and $\delta SF_e(C) = -100$ to -102, $\delta NSF_2(X) = -50.0$ to -51.5, $\delta NS(O)F_2(K) = -45.5$ ppm; J_{AB}, J_{AC}, $J_{BC} \approx 150$, J_{AK}, J_{AX}, J_{CX}, $J_{BK} = 9$—12, J_{BX}, $J_{CK} \approx 1$ Hz.

Mass spectrum: *m/e* (rel. intensities) = 292 M^+ (0), 273 $(M-F)^+$ (12), 254 $(M-F_2)^+$ (3), 235 $(M-F_3)^+$ (1), 216 $(M-F_4)^+$ (1), 184 $NSF_2NSOF_2^+$ (1), 170 $SF_2NSOF_2^+$ (13), 165 $NSFNSOF_2^+$ (0.5), 151 $SFNSOF_2^+$ (3), 135 SF_2NSF^+ (3), 100 $NSOF_2^+$ (70), 89 SF_3^+ (100), 84 NSF_2^+ (65), 81 $NSOF^+$ (43), 70 SF_2^+ (100), 67 SOF^+ (58), 65 NSF^+ (35), 51 SF^+ (43), 48 SO^+ (100), 46 NS^+ (90); mol.-wt.: calc. 292.2, found 289 (cryoscopic in benzene).

Experimental:

(2) from *(1)* and SF_4: SF_4 (8.0 g, 0.08 mol) is condensed with *(1)* (8.4 g, 0.05 mol) and CsF (0.5 g) in an autoclave at -180 °C. After thawing, the mixture is heated at 80 °C and stirred for 5 h. After cooling, the excess of SF_4 is removed at 50 torr and the product is isolated at 0.01 torr in a trap cooled with methanol and Dry Ice. Yield 70%, b. p. 40 °C/20 torr.

(2) from *(3)* and SF_4: SF_4 (10.8 g, 0.1 mol) is condensed with *(3)* (6.0 g, 0.025 mol) and CsF (0.5 g) in an autoclave. After thawing, the mixture is heated at 100 °C and stirred for 12 h. Isolation is as above. Yield 56%.

(5) from *(4)* and SF_4: SF_4 (15 g, two-fold excess) is condensed with *(4)* (13.0 g, 0.07 mol) and CsF (0.5 g) at -180 °C. After thawing, the autoclave is heated to 120 °C and the contents are stirred for 12 h at that temperature. Then, after cooling, the autoclave is opened at 50 torr. Unchanged SF_4 is collected at the temperature of liquid air, and *(5)* and unchanged *(4)* are recovered in a trap cooled with methanol and Dry Ice. The separation is effected by gas chromatography. Yield 30%; b. p. 45 °C/13 torr.

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Dichotomy of C≡C Bonds and Formation of η-Cyclopentadienylchromium Complexes

By *Horst Benn*, *Günther Wilke*, and *Dieter Henneberg*[*]

In Memory of Karl Ziegler

In 1959 it was reported[1] that bis(hexamethylbenzene)-chromium(I) and -chromium(0) *(1)* is formed during a cyclotrimerization of 2-butyne on a catalyst prepared from CrO_2Cl_2 and $Al(C_2H_5)_3$ which converts butadiene into 1,5,9-cyclododecatriene. The chemical behavior, elemental analysis, and—with certain reservations—the mass spectrum indicated the presence of a bis(arene)-chromium complex. The highest mass observed in the mass spectrum was not that of the molecular ion $m/e = 376$ but $m/e = 349$ ($M^+ - CCH_3$). This appeared to be explainable with the assumption that a C—CH_3 group is cleaved from one of the two hexamethylbenzene ligands during the ionization of *(1)* with formation of pentamethylcyclopentadienyl, *i.e.* of a ligand presumably strongly favored by the chromium atom.

This uncertainty surrounding the structure determination prompted us to reinvestigate the system, for, in the meantime, it has become possible by means of a method described by *Fischer et al.*[2] to synthesize bis(hexamethylbenzene)chromium(0) and to characterize it mass spectrometically on the basis of the molecular ion $m/e = 376$. The findings of our recent investigations have led not only to a reassessment of our previous suggestions regarding structure but also to the discovery of a new kind of phenomenon pertaining to such a system. If crystalline $CrCl_3$ instead of CrO_2Cl_2 is allowed to react with $Al(C_2H_5)_3$ and 2-butyne in benzene or toluene a crystalline, paramagnetic ($\mu_{eff} = 2.99$ μ_B[3]) complex *(2a)* containing aluminum and chromium is obtained in yields >70% (referred to almost quantitative reaction of $CrCl_3$) which, on reaction with $LiAlH_4$ or after hydrolysis with dithionite affords crystalline, paramagnetic ($\mu_{eff} = 1.76$ μ_B) hexamethylbenzene(pentamethylcyclopentenedienyl)chromium(I) *(3)* in yields of 60—70%. *(3)* has been unequivocally characterized on the basis of elemental analysis, paramagnetism, and its mass spectrum (*inter alia* $m/e = 349$) and has been shown to be identical with the compound *(1)* bbtained from CrO_2Cl_2.

The hexamethylbenzene in complexes *(2a)* and *(3)* is formed by cyclotrimerization of 2-butyne; but how the five-membered ring is formed was at first unclear, *i.e.* at least the origin of a C—CH_3 group remained to be clarified. A possible explanation was that the reduction of $CrCl_3$ with $Al(C_2H_5)_3$ gives rise to formation of intermediary Cr—C_2H_5 groups, which, by twofold abstraction of an α-H atom[4] are converted into Cr—C—CH_3 systems that finally react with two 2-butyne molecules to give pentamethylcyclopentadienyl.

Such a route, however, could be clearly ruled out by corresponding experiments with $Al(CH_3)_3$ and $Al(C_3H_7)_3$, in

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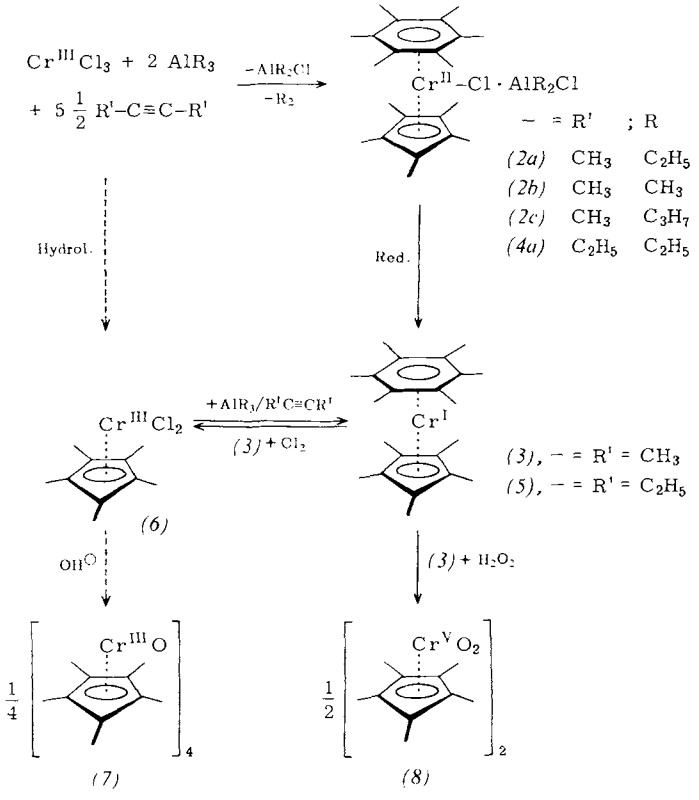
which *(3)* is likewise formed in high yields as end product, for, in these cases CH- and C—C_2H_5 groups instead of a C—CH_3 group would be incorporated into the five-membered ring. The intermediates *(2b)* and *(2c)* differ from *(2a)* only in that they contain $Al(CH_3)_2Cl$ and $Al(C_3H_7)_2Cl$ instead of $Al(C_2H_5)_2Cl$.

On the basis of these findings the formation of the five-membered ring can be explained only on the assumption that a butyne molecule is halved at the C≡C bond[5], each of the two halves then reacting with a further two molecules of butyne with ring closure. Further, conclusive evidence for this route was provided by the analogous reaction of 3-hexyne, which also undergoes cleavage at the C≡C bond with formation of the chromium(II) complex *(4a)*, which can be reduced to hexaethylbenzene(pentaethylcyclopentadienyl)chromium(I) *(5)*. *(5)* was characterized by elemental analysis, its mass spectrum ($m/e = 503$), and its paramagnetism ($\mu_{eff} = 1.73\ \mu_B$).

To our knowledge this is the first case of a high-yield scission of a C≡C bond. We refer to this phenomenon as dichotomy[6].

With the old method in which CrO_2Cl_2 is employed, *(3)* is obtained in yields of, at most, 5—10%, whereas with crystalline $CrCl_3$ the yields are >70%. We presume that the ordered surface of the $CrCl_3$, or of the initial reduction product with $Al(C_2H_5)_3$, plays a decisive role here and that the dichotomy possibly follows formation of a complex of one butyne molecule with two chromium atoms situated a certain distance apart from each other on the surface. Evidence for this is provided by the fact that deep blue, crystalline pentamethylcyclopentadienylchromium chloride *(6)* can be isolated as a minor product on working up the reaction mixture; that is, formation of the five-membered ring takes place first and only after further reduction is the six-membered ring formed and complexed. Thus, in this sense, *(6)* reacts with $Al(C_2H_5)_3$ and 2-butyne to give *(2a)* and *(3)*. The paramagnetic complex *(6)*[7] is soluble both in hydrocarbons and in water and can be salted out of the aqueous phase by NaCl. *(6)* can also be formed from *(3)* and chlorine.



A further by-product which we have obtained on working up the reaction mixture (cf. reaction scheme) is, according to the mass spectrum, a tetrameric pentamethylcyclopentadienylchromium oxide *(7)* ($[C_{10}H_{15}OCr]_4$, $m/e = 182$), whose structure is possibly similar to that of a previously reported cyclopentadienylchromium oxide[8]. In this connection it is also of interest to note that treatment of *(3)* with H_2O_2 leads to cleavage of hexamethylbenzene and conversion into a dimeric pentamethylcyclopentadienylchromium dioxide *(8)* ($[C_{10}H_{15}O_2Cr]_2$, $m/e = 438$).

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[5] This possibility was first discussed in this connection by *R. Köster*.
[6] Dichotomy from the Greek διχοτομία = halving.
[7] *(6)* shows unusual magnetic properties. The susceptibility increases only slightly with decreasing temperature (293 °K; 4.2 μ_B, 143 °K: 3.1 μ_B).
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Stabilization of Monomeric Dichlorogermylene

By *Peter Jutzi, Hans Joachim Hoffmann, David John Brauer*, and *Carl Krüger*[*]

In Group IVB, the stability of divalent compounds increases from carbon to lead owing to known criteria. Thus in contrast to dichlorocarbene, dichlorogermylene is stable under normal conditions; however, except for a dioxane adduct[1], it exists as a polymer of unknown structure. We now report the stabilization of monomeric dichlorogermylene by complex formation with aromatic nitrogen bases.

Whereas organotrichlorogermanes undergo a reaction analogous to transsilylation[2] with 1,3-benzothiazol-2-yltrimethylsilane *(1)*, forming di- and tribenzothiazol-2-ylgermanes[3], we observed uniform and quantitative addition to the C=N bond on reaction of trichlorogermane with *(1)*, affording 2,3-dihydro-2-trimethylsilyl-2-trichlorogermylbenzothiazole *(2)*: ^{1}H-NMR (in $CDCl_3$, TMS internal): δ_{N-H} 14.43 ppm, variable (1); $\delta_{aromatic\,H}$ 7.67—8.94 ppm, M (4); $\delta_{Si(CH_3)_3}$ 0.85 ppm (9). IR (in Nujol): $\nu_{N-H} = 3200$, $\delta_{Si(CH_3)_3} = 1255$, $\nu_{GeCl_3} = 320$, 270 cm^{-1}. M. W.: calc. 387.27, exp. (in C_6H_6) 350.

(2) decomposes exothermally at 91 °C[3a] with liberation of trimethylchlorosilane; from the residue we obtained the dichlorogermylene-benzothiazole adduct *(3)* in 75%

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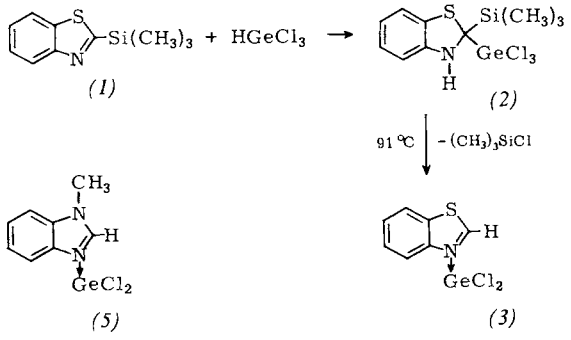
yield after recrystallization from benzene as colorless crystals of m.p. 131 °C.

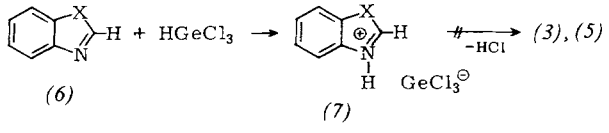


(3) proves surprisingly resistant to hydrolysis and to be thermally stable, dissolving readily in anhydrous ethanol, ethylene bromide, and chloroform, and moderately in benzene. Molecular-weight determinations (in $(CH_2)_2Br_2$) confirm the monomeric structure *(3)*; the monomeric molecular ion with the expected isotopic distribution also occurs as the uppermost peak in the mass spectrum.

The ^{1}H-NMR spectrum (in $CDCl_3$, TMS internal) of *(3)* exhibits signals typical of the benzothiazole skeleton: a multiplet at 7.67—8.68 ppm (4) and a singlet for C^2—H at 10.17 ppm (1). The IR spectrum (in Nujol, 4000—250 cm^{-1}) is almost superimposable upon that of free benzothiazole, the additional bands at 350 and 295 cm^{-1} being assigned to Ge—Cl stretching vibrations.

In the reaction of trichlorogermane with *N*-methylbenzimidazol-2-yl-trimethylsilane *(4)* we have not isolated the initial addition product[4] since in this case the loss of trimethylchlorosilane occurs already at room temperature, with immediate formation of dichlorogermylene-*N*-methylbenzimidazole adduct *(5)*: m.p. 172 °C (dec.); ^{1}H-NMR (in $CDCl_3$, TMS internal): $\delta_{\text{aromatic H}}$ 7.43—8.10 ppm (4); δ_{C^2-H} 9.05 ppm (1), δ_{NCH_3} 4.09 ppm (3); M.W. 276 (mass spectrum).

Synthesis of $GeCl_2$ adducts *via* the non-silylated heterocycles *(6)* is impossible since no addition to the C=N bond takes place but instead protonation to give the thermally stable immonium salts *(7)*.



X = S, NCH_3

The structure of *(3)* (cell data: $a = 15.276(6)$, $b = 8.108(3)$, $c = 8.260(3)$ Å; $\beta = 109.52(3)°$; space group $P2_1/c$; $Z = 4$; $d_{calc.} = 1.92$ g cm^{-3}) was determined by three-dimensional X-ray structure analysis.

From the 4227 reflections recorded by a computer-controlled diffractometer (Mo-Kα, $\lambda = 0.71069$ Å), 2112 structure amplitudes corrected for absorption effects ($\mu = 40.5$ cm^{-1}) were derived, 193 measurements being regarded as unobserved ($I > 2\sigma(I)$). The molecular structure was established by the heavy atom method; least-squares refinement of the atomic parameters (isotropic for H, anisotropic for all other atoms) led to an *R* value of 0.037.

The bond angles at the threefold coordinated germanium are about 90°, the distance Ge—Cl and the angle Cl—Ge—Cl resemble those in Cl_2Ge^{II}·dioxane[5] and $Cl_2Ge^{IV}[\pi\text{-}C_5H_5Fe(CO)_2]_2$[6]; however, these values differ consider-

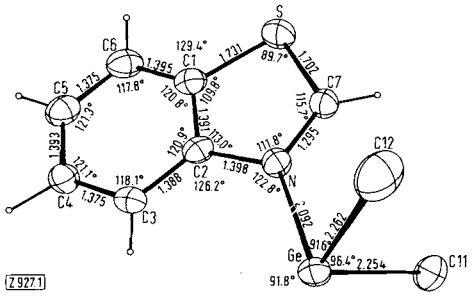


Fig. 1. Perspective representation of 3-dichlorogermylene-1,3-benzothiazole *(3)*. Standard deviations for bond lengths (Å): 0.001 Ge—Cl, 0.002 Ge—N, 0.003 S—C, 0.005 C—N, C—C; for angles (°): 0.1 Cl—Ge—Cl, N—Ge—Cl, all other angles 0.2.

ably from those in $Ge^{IV}Cl_4$ (2.08(2) Å, 109.5°)[7]. The Ge—Cl distances and Cl—Ge—Cl angles in polychlorinated Ge compounds thus reflect not only the oxidation state of the germanium, but also the electronegativity of the coordinated atoms. This finding is in accord with both electron-pair repulsion theory[8] and hybridization theory[9].

The measured Ge^{II}—N distance is 0.13 Å greater than the sum of the covalent radii[10], but 0.10 Å smaller than the Ge^{IV}—N distance in $Cl_4Ge\cdot N(CH_3)_3$[11]. The Ge atom in *(3)* lies 0.168 Å above the plane of the planar (±0.016 Å) benzothiazole skeleton, which bisects the angle Cl—Ge—Cl. The bond length S—C7 is 0.061(4) Å shorter than the corresponding bond length in 2-methylaminobenzothiazole[12]. This finding suggests π-electron delocalization in the five-membered ring, probably with participation of sulfur d orbitals. Adduct formation at the nitrogen does not significantly modify the benzothiazole skeleton. Two short intermolecular distances, between germanium and sulfur (3.618(1) Å) and germanium and chlorine (3.499(1) Å), could be indicative of weak bonding interactions[13].

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Chemical Reactions of Morpholine in a Plasma Discharge

By *Klaus Gorzny* and *Günther Maahs*[*]

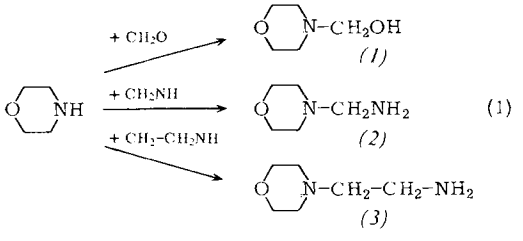
Dedicated to Professor Heinrich Hellmann on the occasion of his 60th birthday

If morpholine is passed through the plasma of a high-frequency glow discharge (27 MHz), reaction proceeds at high conversion rates to yield two main products: dimorpholinomethane and morpholinoacetonitrile. This unexpected reaction course can be explained on the basis of the mass-spectrometric fragmentation pattern of morpholine—a strategy already employed in the interpretation of other plasma reactions[1, 2].

The mass spectrum of morpholine contains the following main peaks[3]:

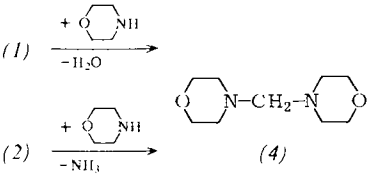
m/e	29	28	57	30	87	56	27	42	43
%	100	74	73	41	36	24	20	15	4

Hence it may be seen that the degradation preferentially generates CH_2O and CH_2NH, and to a lesser extent, $CH_2—CH_2—NH$ fragments. In view of these cleavage products, reaction mechanism *(1)* would appear reasonable.

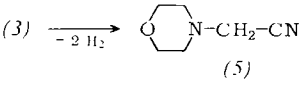


(1)

The intermediates *(1)* to *(3)* are probably in a highly excited state. *(1)* and *(2)* can then undergo further reaction with unreacted morpholine.



In contrast, *(3)* is dehydrogenated to morpholinoacetonitrile *(5)*, since this stabilization appears to be more favorable than the analogous 1,2-dimorpholinoethane formation.



By variation of the reaction parameters pressure and power consumption the reaction course can be controlled at will to produce *(4)* or *(5)* as main product. Thus 95.4% conversion takes place at 0.5—1 torr and 150—200 W to give 138 g/kWh of *(4)* and 14 g/kWh of *(5)*, whereas at 2 torr and 150—300 W conversion is about 80% to give 15 g/kWh of *(4)* and 125.5 g/kWh of *(5)*. A small amount (up to 8 g/kWh) of β-morpholinopropionitrile could be detected as minor product.

The experiments were carried out in quartz glass apparatus with capacitative coupling to a high-frequency generator[2, 4]. The reaction mixture was collected in low-temperature traps and analyzed by gas chromatography. The output was vacuum fractionated to isolate and identify the main products. *(4)*: b.p. 115—120 °C/3 torr, $n_D^{20} = 1.4802$; *(5)*: m.p. 59—60 °C (from methanol). The structures of *(4)* and *(5)* were established by IR, NMR, and mass spectrometry.

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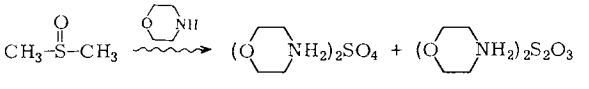
Chemical Reactions of Dimethyl Sulfoxide in a Plasma Discharge

By *Klaus Gorzny* and *Günther Maahs*[*]

Dedicated to Professor Heinrich Hellmann on the occasion of his 60th birthday

Dehydrodimerizations, cyclizations, and eliminations are the preferred reactions under the conditions of a low-pressure high-frequency glow discharge[1]. Only a few examples are known of reactions in which a reactive species generated in the plasma is scavenged by another molecule to give a main product[1, 2].

Morpholine is a particularly suitable scavenger for plasma-generated reactive intermediates[2]. For instance, if morpholine is passed with dimethyl sulfoxide through the plasma of a glow discharge, a mixture of morpholinium sulfate and thiosulfate is formed in yields of up to 163 g/kWh, alongside gaseous products which were not further investigated. The same products are also obtained when the morpholine is added behind the plasma zone, thus confirming the scavenger action of morpholine.



Dimethyl sulfoxide decomposes, both in the presence of light[3] and in the mass spectrometer[4], to give methyl and methylsulfinyl radicals. An analogous fragmentation may also be expected in a plasma[1, 2]. However, no products arising form these intermediate fragments, *e.g.* 4-Methylsulfinylmorpholine, could be detected in the reaction mixture. It may therefore be concluded that the SO—CH_3 fragment is unstable under plasma conditions and decomposes further to SO and CH_3 fragments, the SO fragment undergoing stabilization to sulfate and thiosulfate ion.

The reaction of dimethyl sulfoxide and aniline proceeds analogously but in poorer yield (up to 54.5 g/kWh).

Optimum results (for apparatus see ref.[2]) were obtained at pressures of 0.4—1 torr and power consumptions between 50 and 150 W. The products were characterized by elemental analysis and on the basis of their IR, NMR,

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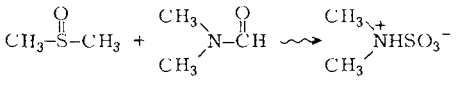
and mass spectra. The composition of the mixtures varied between wide limits: the proportion of sulfate was 10—50% and that of thiosulfate 50—90%; in addition, small amounts of sulfite were also detectable in all cases.

The reaction of dimethyl sulfoxide with formamide takes a completely different course. In the plasma, the reactants yield dimethylamidosulfuric acid (0.4—4.0 torr, power consumption 100—150 W; yield *ca.* 5 g/kWh; m.p. (dec. 161 to 163 °C) alongside unidentified gaseous products. This product is not formed when one of the two reactants is added behind the plasma zone, and must therefore arise from the combination of reactive species of both components.



To our knowledge this is the first example of a plasma synthesis in which a product is formed from fragments of two different organic molecules.

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Tetrakis(η-cyclopentadienyl)tetranickel Trihydride—An Unusual Tetranuclear Cluster

By *Jörn Müller*, *Horst Dorner*, *Gottfried Huttner*, and *Hans Lorenz*[*]

Reduction of dimeric cyclopentadienylnitrosylcobalt with $LiAlH_4/AlCl_3$ produces diamagnetic tetrameric cyclopentadienylcobalt hydride[1], $[C_5H_5CoH]_4$ *(1)*, a tetranuclear cluster with μ_3-hydrido bridges. In order to test whether this kind of reaction is suitable as a general synthetic route for the preparation of cyclopentadienylmetal clusters we subjected dimeric cyclopentadienylnitrosyliron[2], $[C_5H_5FeNO]_2$ *(2)*, as well as cyclopentadienylnitrosylnickel[3], C_5H_5NiNO *(3)*, to the action of the above reducing agent in tetrahydrofuran (THF) at 20 °C. Complex *(2)* afforded exclusively ferrocene. Chromatography of the product mixture obtained from the reaction of *(3)* afforded nickelocene and a compound having the composition $C_{20}H_{23}Ni_4$ *(4)*.

The blackish violet crystals of *(4)* dissolve readily in benzene and THF, less readily in pentane, and do not melt below 320 °C when heated under nitrogen. Its solutions are air-sensitive.

In the mass spectrum of *(4)* the molecular ion appears at *m/e* 495 (based on ^{58}Ni) and exhibits an isotopic distribution characteristic of four Ni atoms. Apart from species arising from loss of up to three H atoms, the 50-eV spectrum contains the ions $C_{15}H_{15}Ni_4^+$, $C_{10}H_{10}Ni_2^+$, $C_{10}H_{10}Ni^+$, $C_5H_5Ni^+$, and Ni^+ as characteristic fragments. Prolonged residence of the sample in the ion source results in gradual decomposition with liberation of H_2 and in partial degradation of the Ni_4 unit; 12-eV spectra reveal that the complexes $C_{20}H_{22}Ni_4$, $C_{20}H_{21}Ni_4$, and $C_{20}H_{20}Ni_4$ are also formed as thermolysis products in addition to nickelocene.

The IR spectrum (KBr pellet) of *(4)* indicates the presence of π-bonded symmetrical cyclopentadienyl ligands; the following bands appear (the corresponding absorptions of nickelocene are given in paratheses for comparison): 3098 (3095), 1420 (1425), 1332 (1332), ≈1270 (1261), 1108 (1111), 1050 (1046), 999 (1000), 800 (798), 770 (768), 342 (357) cm^{-1}. The paramagnetic compound also gives a ^1H-NMR spectrum with a very broad signal at $\tau = 157$ (in THF) which can also be assigned to cyclopentadienyl protons. Accordingly, compound *(4)* is to be regarded as tetrakis(η-cyclopentadienyl)tetranickel trihydride $[C_5H_5Ni]_4H_3$. In contrast to *(1)*, no ν_{NiH} absorption can be recognized in the IR spectrum, which, however, cannot be construed as contraindicating the presence of metal hydride groups[4].

The structure of *(4)* was proved by X-ray analysis[5]. Crystal data: space group C2/c; $a = 2832 \pm 2$, $b = 923 \pm 1$, $c = 1503 \pm 1$ pm; $\beta = 102.77 \pm 0.08°$; $V = 3831 \pm 10 \times 10^6$ pm^3; $d_{calc.} = 1.726 \pm 0.005$, $d_{exp.} = 1.78 \pm 0.05$ g cm^{-1}; $Z = 8$; $R_1 = 0.064$ for 1227 independent nonzero structure factors.

The molecule consists of a slightly distorted Ni tetrahedron having a π-bonded cyclopentadienyl ring at each corner (average distances: Ni—Ni 246, Ni-ring center 177.7, Ni—C 210, and C—C_{ring} 138 pm). The hydride hydrogen atoms could not be directly located in the electron density diagram of a difference Fourier synthesis; however, their positions could be deduced from the deviations of the molecule from strictly tetrahedral symmetry. The rings (C21 ... C25), (C31 ... C35), and (C41 ... C45) form angles with the basal face Ni2—Ni3—Ni4 that are significantly smaller than the corresponding angles formed by all the rings with the other tetrahedral faces, *i.e.* an average of 63.4° compared with 73.0°. The prevailing steric conditions can be interpreted by assuming that the three H atoms act as

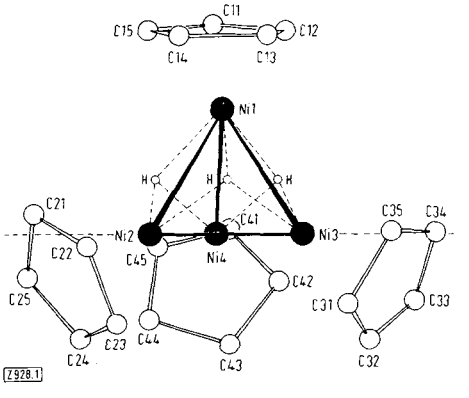

Fig. 1. Schematic representation of the molecule $[C_5H_5Ni]_4H_3$ *(4)*; projection perpendicular to the Ni2—Ni3—Ni4 plane.

μ_3 bridges across three tetrahedral faces. This is in accord with the elongation of the Ni—Ni distances by *ca.* 10 pm compared to Ni—Ni single bonds[6].

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The dipole moment of 2.0±0.1 D measured in benzene is also in accord with the deviation of the structure of *(4)* from an ideal tetrahedron.

In contrast to *(1)*, compound *(4)* exceeds the noble gas rule. Tetrahedral $[C_5H_5Ni]_4$ would be isoelectronic with *(1)* and therefore diamagnetic. The three hydride hydrogen atoms in $[C_5H_5Ni]_4H_3$ supply three additional electrons. It is, however, remarkable that no spin pairing takes place in the complex; instead, magnetic measurements both by the Gouy method (77°K: $\chi_g = 44.35 \times 10^{-6}$ cm^3 g^{-1}, $\mu_{eff} = 3.72 \pm 0.08\ \mu_B$; 295°K: $\chi_g = 13.84 \times 10^{-6}$ cm^3 g^{-1}, $\mu_{eff} = 4.10 \pm 0.08\ \mu_B$; χ_g independent of field) and by the ^{1}H-NMR shift method ($\mu_{eff} = 4.10 \pm 0.1\ \mu_B$) indicate the presence of three unpaired electrons. No explanation of the observed paramagnetism and its temperature independence has yet been forthcoming; accidental orbit degeneracy may be present.

(1) and *(4)* are the first organometallic tetranuclear clusters containing only hydrogen and cyclopentadienyl as ligands. All other known cyclopentadienyl-metal clusters having four and more directly linked metal atoms are stabilized by carbonyl or hetero ligands in addition to C_5H_5 ligands. Attempts to prepare the hydride-free complex $[C_5H_5Ni]_4$ which appears at least momentarily under thermolytic conditions in the mass spectrometer, have so far been unsuccessful. For instance, mild oxidation of *(4)* with a substoichiometric quantity of iodine in pyridine yielded merely nickelocene and NiI_2 (as pyridine adduct) as well as pyridinium iodide. This finding suggests that the stability of the nickel cluster is largely due to the hydride bridges.

Procedure:

All operations must be carried out under nitrogen.

A solution of *(3)* (2 ml, 20 mmol) and $AlCl_3$ (2.7 g) in THF (80 ml) is slowly added dropwise to one of $LiAlH_4$ (0.76 g, 20 mmol) and $AlCl_3$ (2.7 g) in THF (110 ml), the color changing from dark red to blackish green. After 2 hours' stirring, the reaction mixture is hydrolyzed with water (200 ml) with ice-cooling and extracted with ether. The ether phase is washed with $NaHCO_3$ solution, dried over Na_2SO_4, and the ether is drawn off. The black residue is dissolved in benzene and Al_2O_3 (Woelm, 10% H_2O) is added until the solution has been completely absorbed, the benzene then being drawn off. The dark green solid mixture is placed in the head of a chromatography column (2 cm diam., 80 cm length) packed with Al_2O_3 (Woelm, 6% H_2O) in pentane. Nickelocene and unreacted *(3)* are first eluted with pentane, and then *(4)* as a dark green zone with benzene. Removal of the benzene and recrystallization from ether/pentane (1:3) at low temperature affords 150 mg of *(6)* in analytically pure form.

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5-Substituted Ethyl 2-Thiazoline-4-carboxylates

By *Ulrich Schöllkopf* and *Dieter Hoppe*[*]

Ethyl 2-thiazoline-4-carboxylates[1,2] of type *(4)*, unsubstituted at position 2, are of interest for synthesis of penicillin derivatives[2]. We have found that they are obtained in good yield and relatively pure if a solution of an ethyl 2-isocyanoacrylate *(1)*[3] and *ca.* 10 mol-% of a weak base (such as triethylamine or pyridine) in chloroform is saturated with hydrogen sulfide at 20—40 °C and the mixture is then distilled.

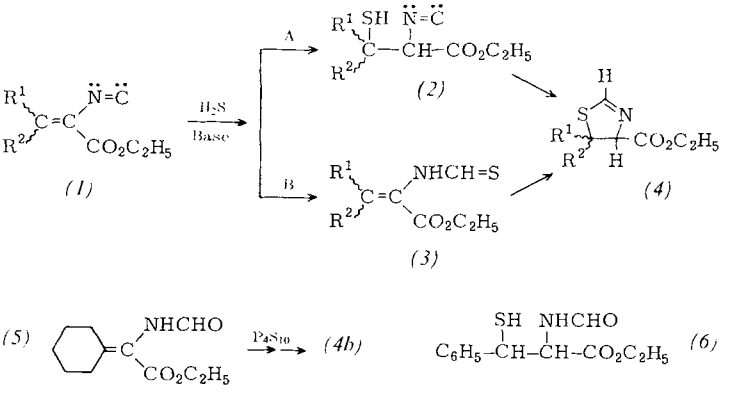

Table 1. Ethyl 2-thiazoline-4-carboxylates *(4)* synthesized from ethyl 2-isocyanoacrylates *(1)*.

(4)	R^1	R^2	Yield [%]	B.p. [C/torr]	*trans*: *cis* [a]	^{1}H-NMR (CCl_4) [τ]
a	CH_3	CH_3	80	80–81/0.1	–	8.3 and 8.65 (CH_3), 2.05 (d, 2-H), 5.55 (d, 4-H)
b	$-(CH_2)_5-$		78	100–102/ 0.05	–	2.00 (d, 2-H), 5.50 (d, 4-H)
c	$(CH_3)_3C$	H	83	95–98/0.3	4:1	*trans*: 1.95 (d, 2-H), 5.28 (q, 4-H), 5.97 (d, 5-H); *cis*: 2.13 (d, 2-H), 5.12 (q, 4-H)
d	C_6H_5	H	100[b]	not determined	3:1 [d]	*trans*: 2.03 (d, 2-H), 5.82 and 8.75 (q and t, resp., C_2H_5), 4.98 (q, 4-H), 4.75 (d, 5-H); *cis*: 1.90 (d, 2-H), 6.30 and 9.20 (q and t, resp., C_2H_5)
e	2-furyl	H	80	115–120/ 0.1	6:1	*trans*: 2.02 (d, 2-H), 4.80 (q, 4-H), 4.60 (d, 5-H); *cis*: 1.85 (d, 2-H)
f	C_6H_5	C_6H_5	–[c]			

[a] Isomer ratio determined by NMR spectroscopy.
[b] Crude product.
[c] 72% of the thioformamide *(3f)*, m. p. 154 °C, was isolated (see text).
[d] The ratio can be increased to *ca.* 9:1 on subsequent equilibration by 10 mol-% of sodium ethoxide in ethanol (1 h, 20 °C).

The reaction probably proceeds mainly by route A, *i.e.* by base-catalyzed addition of hydrogen sulfide to the activated double bond of *(1)*, yielding β-mercapto isocyanides *(2)* which cyclize to *(4)*. In an experiment with *(1d)* the intermediate *(2d)* was detected by IR spectroscopy

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(band at 2150 cm^{-1}). Apparently, the extent to which reaction proceeds by route B depends on the nature of R^1 and R^2; by this route, the hydrogen sulfide adds first to the isocyanide group, yielding the thioformamide *(3)* which then undergoes ring closure to *(4)*. Formation of the non-cyclizing ethyl 3,3-diphenyl-2-(thioformylamino)acrylate *(3f)* from *(1f)* and hydrogen sulfide shows that formation of thioformamides cannot be disregarded.

The 2-thiazoline-4-carboxylic esters *(4)* are formed also, although in less pure state, on reaction of ethyl 3-substituted 2-(formylamino)acrylates[4] with tetraphosphorus decasulfide; *e.g.* we obtained 50% of *(4b)* when we heated ethyl 2-cyclohexylidene-2-(formylamino)acetate *(5)* in benzene with P_4S_{10} for 5 h; optimization of the procedure and exploration of its scope are in progress because this may be a more convenient method of preparing large amounts of *(4)* since the conversion of the 2-(formylamino)acrylic ester[4] into *(1)*[3] becomes unnecessary.

In preliminary experiments the thiazolinecarboxylic esters *(4)* were readily hydrolyzed to β-substituted *N*-formylcysteine esters[5]. For example, we obtained *N*-formyl-β-phenylcysteine ethyl ester *(6)* when *(4d)* was chromatographed on neutral silica gel in moist ether. This identifies a simple synthesis of *S*-unprotected β-substituted cysteines. *(6)* was obtained as a mixture of diastereoisomers; one isomer was obtained pure by recrystallization from ether [m. p. 91 °C; ^{1}H-NMR ($CDCl_3$): τ = 1.90 and 3.45 (s and br. d, resp.; NH—CHO); 7.80 (d, SH, $J_{3\text{-H/SH}} = 6$ Hz); 4.85 (q, 2-H, $J_{2\text{-H/NH}} = 10$ Hz, $J_{2\text{-H/3-H}} = 6$ Hz); 5.50 (t, 3-H); 2.70 (C_6H_5); 4.85 and 8.80 (q and t, resp., OC_2H_5). IR (KBr): ν = 3230 (NH), 2550 (SH), 1720 (C=O), 1650 (CH=O) cm^{-1}].

Ethyl 5,5-dimethyl-2-thiazoline-4-carboxylate (4a)

Hydrogen sulfide is passed into a solution of *(1a)*[3] (6.8 g, 44.5 mmol) and triethylamine (0.5 g, 5.0 mmol) in chloroform (10 ml) with stirring at 20—40 °C until the isocyanide band at 2120 cm^{-1} is no longer detectable. The solvent is removed in a rotatory evaporator at water-pump vacuum and the residue distilled. This affords *(4a)* (6.6 g, 80%); IR (film): ν = 1560 (C=N), 1725 and 1740 (C=O) cm^{-1}. (Similar IR bands are also observed for other compounds *(4)* but without splitting of the carbonyl frequency.)

Ethyl cyclohexanespiro-5'-(2'-thiazoline-4'-carboxylate) (4b)

(5)[4] (6.3 g, 30 mmol) is heated in benzene (30 ml) with finely powdered P_4S_{10} (1.45 g, 3.0 mmol) for 5 h under reflux. The solution is then decanted and the solvent is removed in a rotatory evaporator in a vacuum. Distillation finally affords *ca.* 90%-pure *(4b)* (yield 3.8 g, 55%), giving the same NMR spectrum as an authentic sample (see above).

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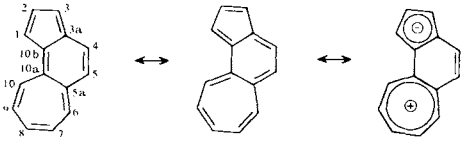
Stable Phenazulene Derivatives by [12+2]Additions to 8,9-Dicyanosesquifulvalene[1][**]

By *Horst Prinzbach* and *Heinz-Walter Schneider*[*]

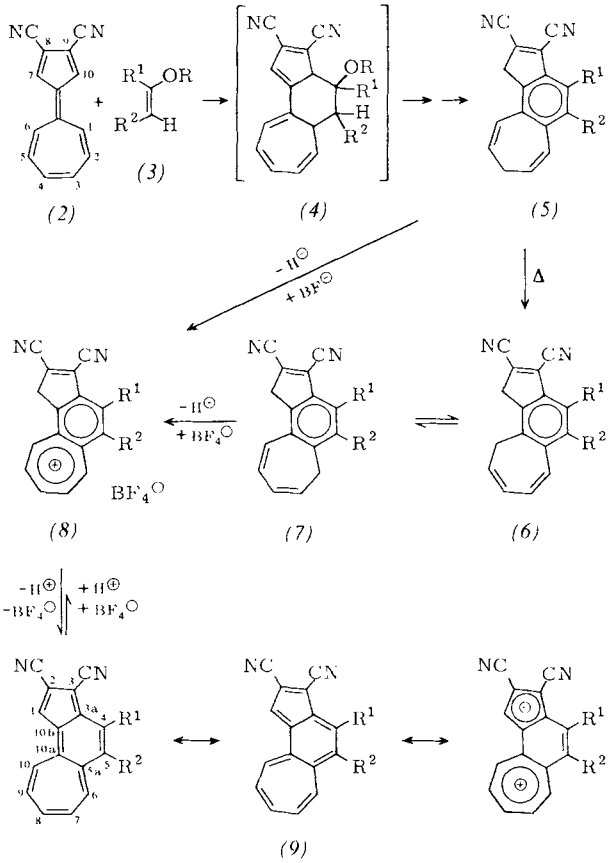
The $C_{14}H_{10}$ hydrocarbon phenazulene *(1)*[2] (cyclohept-[*e*]indene) is a 14π-perimeter molecule, which because of the transannular bonds between C-3a and C-10b and between C-5a and C-10a can be regarded as a higher homolog of azulene[3]. In accord with the π-electron density distribution indicated by the limiting structures, a significant resonance stabilization and a considerable polarity has been postulated for this conformationally rigid [14]annulene[4].

After earlier attempts at synthesis had proved fruitless[5], we have obtained derivatives of *(1)* *via* [12+2]addition to 8,9-dicyanosesquifulvalene *(2)*[6]. The compound *(2)*



(1)

is resistant to electron-deficient dienophiles but reacts quantitatively with the enol ethers *(3a)* and *(3b)* [510 mg (2.5 mmol); 5 mmol of *(3)*, R = C_2H_5] in bromobenzene (200 ml) at 150 °C (3 h); the adducts *(4a)* and *(4b)* rapidly



a, R^1-R^2 = $-(CH_2)_4-$; *b*, R^1 = C_6H_5, R^2 = H

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lose alcohol and, by migration of hydrogen, afford mixtures of the isomeric dihydrophenazulenes *(5a)*—*(7a)* and *(5b)*—*(7b)*, respectively[8]. With weak bases such as pyridine these products give anions smoothly, but because of very rapid addition of conventional hydride-eliminating reagents, these anions are not suitable precursors of *(9a)* and *(9b)*.

Hydride elimination can be achieved by means of trityl tetrafluoroborate (CH_2Cl_2; 20°C), smoothly from *(5a)* and *(5b)*, but very much more slowly from *(6a)* and *(6b)* or *(7a)* and *(7b)*, yielding the phenazulenium salts *(8a)* and *(8b)*. These salts are very acidic, so that *(8b)* is deprotonated to a considerable extent under the conditions of its preparation [21% based on *(5b)*—*(7b)*], and the isolated *(8a)* is deprotonated to *(9a)* by the action of weak bases (pyridine) [93% based on *(8a)*]. Without isolation of intermediates *(5a)*—*(7a)* are oxidized to *(9a)*, and *(5b)*—*(7b)* to *(9b)*, by chloranil or dichlorodicyanobenzoquinone (CH_2Cl_2; 20°C), though the latter reagent rapidly reacts further with *(9a)* and *(9b)*[9].

Table 1. Physical data for compounds *(8a)*, *(9a)*, and *(9b)*.

Cpd. [a] M.p. [°C] M^+ [m/e]	UV λ_{max} [nm] (ε)	NMR (τ)
(8a)	268 (18700), 298 (17900), 327 (19500), 342 (20100), 378 (16000), 406 (23300), 500 (sh, 3080), 580 (sh, 2340), [b]	−0.3–0.3 (m, 6-H, 10-H), 0.6–1.2 (m, 7-H–9-H), 5.06 (s, 21-H), 6.1–6.65 (m, α, α′-CH_2), 7.65–8.0 (m, β,β′-CH_2) [c]
(9a) 272–273 282	252 (27800), 292 (sh, 25400), 305 (26900), 339 (sh, 8350), 386 (sh, 20000), 410 (26200), 567 (6750), 680 (sh, 2900) [d]	0.55–0.8 (m, 10-H), 1.0–1.2 (m, 6-H), 1.9–2.2 (m, 7-H–9-H), 2.12 (s, 1-H), 6.3–6.5 (m, α-CH_2), 6.7–6.9 (m, α′-CH_2), 7.9–8.15 (m, β,β′-CH_2) [e]
(9b) 241–242 304	241 (36100), 286 (29100), 382 (26400), 404 (29400), 576 (7600), 700 (sh, 4800) [d]	0.5–0.7 (m, 10-H), 1.2–1.35 (m, 6-H), 1.8–2.15 (m, 7-H–9-H), 1.94 (s, 1-H), 2.2–2.5 (m, 5-H, C_6H_5) [e]

[a] Correct elemental analyses were obtained for the compounds isolated. The numbering of *(9b)* is retained for *(8a)* and *(9a)*.
[b] In H_2SO_4/CH_3COOH.
[c] In CF_3COOH.
[d] In CH_2Cl_2.
[e] In $CDCl_3$.

In accord with the low basicity of *(2)* and the high acidity of the salts *(8)*, the deep blueish-violet, extremely sparingly soluble phenazulenes *(9a)* and *(9b)* are only very weakly basic, although they can be reprotonated to *(8a)* and *(8b)* by conc. H_2SO_4 in glacial acetic acid (UV concentration measurement). The UV, IR, ^{1}H-NMR[10], and MS data, as well as some subsequent reactions[9], accord with the structures *(8)* and *(9)*. For *(9a)* the assignment of 6-H, 10-H, and for *(9b)* assignment of 1-H, 5-H, was made according to the calculated π-electron density at their respective carbon atoms (see [4]). The lower of the α,α′-CH_2 signals from *(9a)* was assigned to that CH_2 group which was attached to the C atom with the lower π-density.

Irrespective of such uncertainties and of the influence of substituents, the chemical shifts of the perimeter protons of *(9a)* and *(9b)*—particularly in comparison with the shifts of the perimeter protons of *(2)*, *(5a)*—*(7a)*, *(5b)* to *(7b)*, and *(8a)*—as well as the shifts of the α,α′-CH_2 protons of *(9a)* [τ = 6.3–6.5; 6.7–6.9; to be compared with 6.6–7.4 for *(6a)*, *(7a)*] may well indicate[11] the existence of a diamagnetic ring current in *(9a)*, *(9b)* and a polarity that is increased by the CN groups[12]. A strongly polar ground state is also indicated by the strongly negative solvatochromism in the electron spectrum of *(9a)* [λ_{max} (CH_3CN): 660 sh, 550, 400, 302, 250 nm; (CCl_4): 772 sh, 718, 597, 420, 310, 276 nm].

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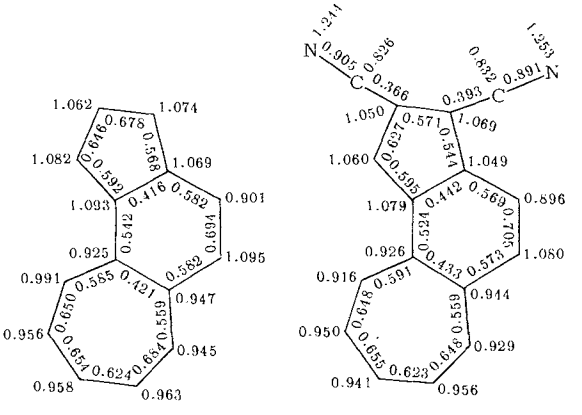
[1] Cyclic Cross-Conjugated Bond Systems, Part 26.—Part 25: *H. Sauter* and *H. Prinzbach*, Angew. Chem. *84*, 297 (1972); Angew. Chem. internat. Edit. *11*, 296 (1972).

[2] This trivial name (from phenanthrene-azulene) was chosen in analogy to the designation "anthrazulene", shortened from anthracene-azulene, for the linear-fused analog (cyclohept[*f*]indene). After reaction of base with a doubly phenyl-substituted conjugate acid of anthrazulene a product—red in solution—was observed that polymerized rapidly (*D. J. Bertelli*, J. Org. Chem. *30*, 891 (1965); see also *A. D. Campbell* and *S. M. Slater*, J. Chem. Soc. *1952*, 4352).

[3] *K. Hafner* in: The Jerusalem Symposia on Quantum Chemistry and Biochemistry, Vol. 3, Jerusalem Academic Press, Jerusalem 1971, p. 256.

[4] *R. Zahradník*, Angew. Chem. *77*, 1097 (1965); Angew. Chem. internat. Edit. *4*, 1039 (1965); *B. A. Hess, Jr.*, J. Org. Chem. *36*, 3418 (1971); *H.-J. Lindner*, personal communication; see also *T. N. Nakajima*, Fortschr. Chem. Forsch. *52*, 1 (1972); *G. Rasch*, Monatsh. Chem. *100*, 1372 (1969). *R. Zahradník* has placed at our disposal the following PPP data (π-bond orders, π-electron densities, electron spectra and dipole moments) for *(1)* and its 2,3-dicyano derivative:



(1), λ_{max} = 674, 572, 505, 364, 313, 292, 282, 270 nm; μ = 6.2 D; dicyano-*(1)*: λ_{max} = 689, 568, 505, 336, 287, 276, 260, 241 nm; μ = 11.7 D.

[5] Prof. *Bertelli* has kindly informed us that, as with anthrazulene [2], the action of trimethylamine on a diphenylphenazulenium salt led to transient red coloration of the solution and thereafter substantially to polymeric products.

[6] Some alkyl- and aryl-substituted sesquifulvalenes react with tetracyanoethylene in a [12+2]addition (*cis* stereochemistry confirmed by X-ray analysis [7]), but with acetylenedicarboxylic esters (which are more suitable for preparation of phenazulenium derivatives) not in a [6+2]-(*H. Prinzbach* and *H. Knöfel*, Angew. Chem. *81*, 900 (1969); Angew. Chem. internat. Edit. *8*, 881 (1969)), but in a [4+2]-reaction [7] (*V. Blumenstock*, Dissertation, Universität Freiburg 1974).

[7] *R. E. Davis, H. Knöfel, V. Blumenstock*, and *H. Prinzbach*, unpublished work.

[8] We have not attempted separation of the dihydro isomers. The individual positions and multiplicities of the CH_2 protons in the seven-membered ring [*(5a)*, *(5b)*, τ = 7.42, 7.64 (struct. t, *J* = 6.5 Hz); *(6a)*, *(7a)* 7.1 (struct. d, *J* = 6.5 Hz); *(6b)*, *(7b)* 6.85 (struct. d, *J* = 6.5 Hz)] agree well with values reported for other benzotropilidenes (see, *inter alia*, *G. W. Gruber* and *M. Pomerantz*, Tetrahedron Lett. *1970*, 3755; J. Org. Chem. *33*, 4501 (1968).

[9] *H. Prinzbach, L. Knothe*, and *H.-W. Schneider*, Angew. Chem. *85*, 1113 (1973); Angew. Chem. internat. Edit. *12*, 1009 (1973).

[10] We thank Dr. *G. Englert*, Basel, for the 100-MHz-FT spectra.

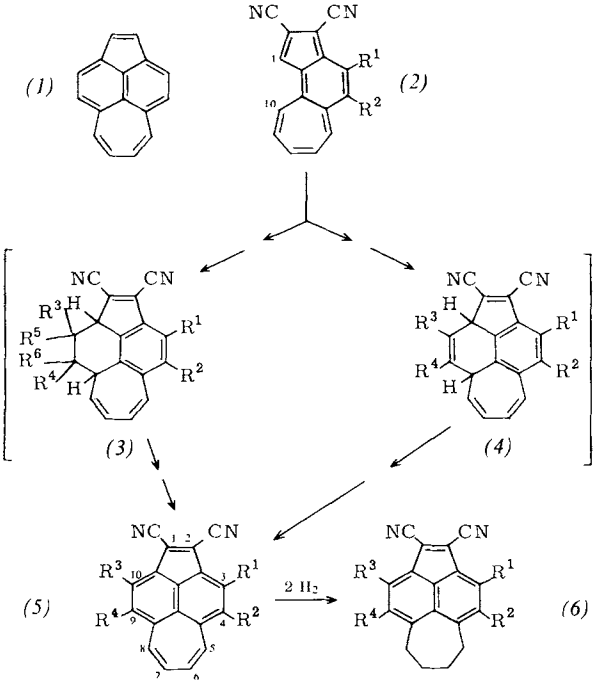
[11] *R. C. Haddon, V. R. Haddon*, and *L. M. Jackman*, Fortschr. Chem. Forsch. *16*, 103 (1971).

[12] *H. Prinzbach, H. Knöfel*, and *E. Woischnik* in: The Jerusalem Symposia on Quantum Chemistry and Biochemistry, Vol. 3, Jerusalem Academic Press, Jerusalem 1971, p. 269.

A New Route to the Acepleiadylene System[1][**]

By *Horst Prinzbach, Lothar Knothe*, and *Heinz-Walter Schneider*[*]

In the synthesis developed by *Boekelheide et al.*[2] for the 14π-perimeter system[3] acepleiadylene *(1)* (cyclohept[*fg*]-acenaphthylene) a five-membered and a seven-membered ring were attached to a given naphthalene skeleton. The reverse route, namely attachment of the six-membered rings to the sesquifulvalene skeleton, has been realized by us for some derivatives. This new type of synthesis is useful for the preparation of specifically substituted derivatives and can be varied within certain limits; it succeeds because the strongly polar 2,3-dicyanophenazulenes *(2)*[11] undergo cycloaddition at positions C-1 and C-10 with both electron-rich and electron-deficient ethylene and acetylene derivatives[4].



Typical of the reactivity of the phenazulenes *(2)* towards enamines is the reaction of *(2a)* with 1-(1-cyclohexenyl)piperidine. When their solutions are mixed (1 : 2 mol, CH_2Cl_2, 20 °C) there is immediate fading of the color towards yellow and on storage—even with exclusion of oxygen—a gradual deepening of the color to reddish-violet. On chromatography on silica gel (CH_2Cl_2) a 42% yield of 1,2-dicyano-3,4:9,10-dicyclohexenoacepleiadylene *(5a)*[5], which crystallizes in reddish-violet needles, can be isolated from the single band that migrates. *(5a)* can also be obtained from *(2a)* and 1-ethoxycyclohexene, but this enol ether usually adds only at higher temperatures (bromobenzene, 150 °C) and these conditions suffice for the phenazulene to undergo subsequent thermal reactions (dimerization?). *(5a)* can also be obtained, without isolation of *(2a)* but in poorer yield (*ca.* 20%), directly from 8,9-dicyanosesquifulvalene and 1-(1-cyclohexenyl)piperidine (1 : 2 mol, CH_2Cl_2, 20 °C). By this convenient procedure we have also prepared the symmetrically substituted acepleiadylenes *(5b)*—*(5d)* in *ca.* 20% yields from the sesquifulvalene with 1-(1-cyclopentenyl)piperidine and with α- and β-styrylpiperidine[7]. As for the precursors of *(2a)*[1], we must leave open the question of possible intermediates such as *(3a)* and the mechanism of the dehydrogenation.

The dicyanophenazulenes also react differently from 8,9-dicyanosesquifulvalenes with electron-deficient reagents such as dimethyl acetylenedicarboxylate (ADM), maleic anhydride (MAA), dichlorodicyanobenzoquinone, chloranil *etc.*; these reactions, however, usually occur sufficiently fast only at 120 °C when competing reaction of *(2)* reduces the yield substantially. From *(2a)* and ADM (120 °C) a 30% yield can be obtained of the product *(5e)*, crystallizing in reddish-violet needles, without any indication of *(4e)* or of disproportionation products. The MAA adduct, obtainable only at 150 °C and in lower yield, was isolated after esterification and was characterized in the same way as *(5e)*.

The course of the reaction with dichlorodicyanobenzoquinone (1 : 2 mol, CH_2Cl_2, 20 °C) is surprising. According to elemental analysis and the mass spectrum, the blueish-violet product (55%), formed even at 20 °C, has the composition $C_{24}H_{12}N_4$ (mol. wt. 356) and spectral data indicate unambiguously the structure *(5f)*. Formulation of *(3f)* as an intermediate is supported by the result with chloranil (bromobenzene, 150 °C); in spite of the distinctly higher temperature there is no fragmentation, but instead, twofold elimination of HCl to yield the acepleiadylene *(5g)* (30%)[6]. The attractive interpretation of the transition *(3f)* → *(5f)* as a retro-Diels-Alder decomposition is excluded: in the presence of methanol there is formed, besides *(5f)*, not dimethyl 2,3-dichlorosuccinate, but dimethyl 2,3-dichloromaleate in 46% yield[8]. The structures of the acepleiadylenes *(5a)*—*(5g)* are proved by spectroscopic data. Also, *(5a)* and *(5d)* were converted selectively into acenaphthylene derivatives *(6a)* and *(6d)* respectively by hydrogenation (CH_2Cl_2, $Pd/CaCO_3$). In agreement with

	R^1	R^2	R^3	R^4	R^5	R^6
a	$-(CH_2)_4-$		$-(CH_2)_4$		H	H
b	$-(CH_2)_3-$		$-(CH_2)_3-$		H	H
c	C_6H_5	H	C_6H_5	H	H	H
d	H	C_6H_5	H	C_6H_5	H	H
e	$-(CH_2)_4-$		CO_2CH_3	CO_2CH_3		
f	$-(CH_2)_4-$		CN	CN	$-COC(CN)=C(CN)CO-$	
g	$-(CH_2)_4-$		$-COC(Cl)=C(Cl)CO-$		Cl	Cl

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PPP calculations[9] the electron spectra of the acepleiadylenes *(5a)*—*(5f)*—all strongly fluorescent—depend little on the nature of the substituents R^1—R^4. Not unexpectedly the UV spectrum of the non-fluorescent *(5g)* is distinctly different.

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[1] Cyclic Cross-Conjugated Bond Systems, Part 27.—Part 26: *H. Prinzbach* and *H.-W. Schneider*, Angew. Chem. *85*, 1112 (1973); Angew. Chem. internat. Edit. *12*, 1007 (1973).

[2] *V. Boekelheide, W. E. Langeland*, and *C.-T. Liu*, J. Amer. Chem. Soc. *73*, 2432 (1951); *V. Boekelheide* and *G. K. Vick*, *ibid. 78*, 653 (1956).

[3] *A. J. Jones, P. D. Gardner, D. M. Grant, W. M. Litchman*, and *V. Boekelheide*, J. Amer. Chem. Soc. *92*, 2395 (1970).

[4] For the segment C^1—C^{10b}—C^{10a}—C^{10} a "butadienoid character order" (*O. E. Polansky* and *G. Derflinger*, Internat. J. of Quantum Chemistry, Vol. I, 379 (1967)) of $\rho = 0.7005$ has been calculated (*O. E. Polansky*, personal communication).

[5] With comparable ease *(2a)* reacts with α- and β-styrylpiperidine to give unsymmetrically substituted acepleiadylenes [6]; see also the addition of ADM to pyridiniocyclopentadienylides (*R. Gompper*, Angew. Chem. *81*, 348 (1969); Angew. Chem. internat. Edit. *8*, 312 (1969)).

[6] *H.-W. Schneider*, Dissertation, Universität Freiburg 1973.

[7] In contrast thereto, addition of 1-(1-propenyl)piperidine and of methyl 3-piperidinocrotonate to *(2c)* is not regiospecific [6].

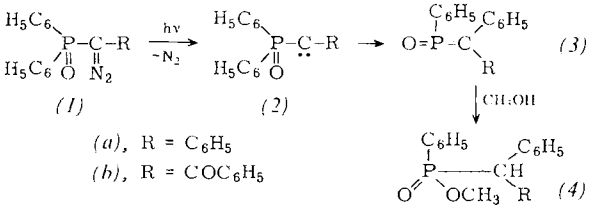
[8] In co-operation with Miss *B. Beijer*, University of Göteborg.

[9] The π-electron densities and π-bond orders calculated for 1,2-dicyanoacepleiadylene deviate only slightly from the values obtained for *(1)* (*R. Zahradník*, personal communication; *R. Zahradník, H. Prinzbach, et al.*, unpublished work).

Detection of Alkylideneoxophosphoranes by Cycloaddition of Carbonyl Compounds[**][1]

By *Manfred Regitz, Hans Scherer, Walter Illger*, and *Helmut Eckes*[*]

Irradiation of (diphenylphosphoryl)diazomethanes *(1)* in methanol affords phosphinic esters *(4)* in amounts that vary with the nature of the group R; their formation is readily explained as occurring by way of the carbene *(2)* and the alkylidenephosphorane intermediates *(3)*[2].

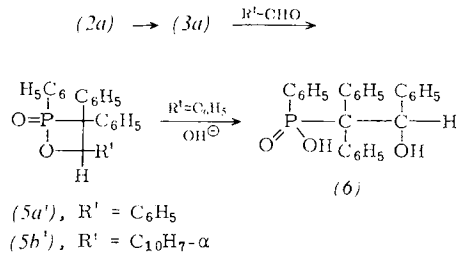


(1) *(2)* *(3)*

(a), R = C_6H_5
(b), R = COC_6H_5

(4)

To trap the hitherto unknown heterocumulenes *(3)*, they were prepared in the presence of carbonyl compounds. On irradiation of *(1a)* in benzene containing benzaldehyde or 1-naphthaldehyde the solvent was first cyclopropanated by the carbene *(2a)*, yielding 7-(*exo*-diphenylphosphoryl)-7-*endo*-phenylnorcaradiene [15% yield; m.p. 179 to 180°C; NMR ($CDCl_3$): δCH-cyclopropane = 3.46, d, $^3J_{H,P}$(*cis*) = 14 Hz[1,3]]. However, at least 18% of *(2a)* was rearranged by a *P/C*-phenyl shift, yielding *(3a)* which undergoes [2+2]-cycloaddition with the aldehydes, thus forming the 1,2-oxaphosphetanes *(5a')* and *(5b')* [m.p. 246 and 249°C, respectively; NMR ($CDCl_3$): δCH-ring

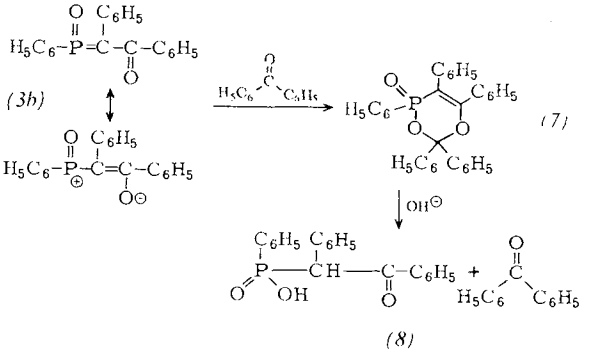


(5a'), R' = C_6H_5
(5b'), R' = $C_{10}H_7$-α

(6)

= 4.8 and 5.0 d, $^3J_{H,P}$ = 23 and 26 Hz, respectively]. A fragment $M^+ - C_6H_5PO_2$ appearing in the mass spectrum of *(5a')* and *(5b')* is not consistent with the alternative orientation of the aldehyde in the cycloaddition. Furthermore, alkaline ring fission of *(5a)* to the β-hydroxy phosphinic acid *(6)* [m.p. 140°C; NMR ($CDCl_3$): δCH-β = 5.42 d, $^3J_{H,P}$ = 8 Hz] accords with the structure assigned to the cycloadducts.

The α-benzoylbenzylideneoxophosphorane *(3b)* is obtained by analogous photochemical reaction in a melt of *p*-dichlorobenzene (60°C), this product being expected because of the 1,4-dipolar reactivity due to the differing electronegativities of phosphorus and oxygen. In agreement therewith, the product [yield 15%; m.p. 182—183°C (from ethyl acetate/ether); no CO absorption in the IR spectrum] trapped by benzophenone has the 1,5,2-dioxaphosphorin structure *(7)*.



(3b) *(7)*

(8)

Thermal fragmentation (215°C, $5 \cdot 10^{-3}$ torr) of *(7)* to diphenylacetylene, benzophenone and the hypothetical fragment $C_6H_5PO_2$[4] also supports formula *(7)*, as does hydrolysis by 20% potassium hydroxide in ethanol/water at room temperature to the phosphinic acid *(8)* [yield 83%; m.p. 148°C; IR (KBr): 2225, 2560 (OH, br), 1675 cm^{-1} (CO); NMR ($CDCl_3$): δCH-α = 5.50 d, $^2J_{H,P}$ = 20 Hz] and benzophenone. On use of acetophenone as trapping agent for *(3b)* there is formed, analogously to *(7)*, a 30% yield of an oily mixture of diastereoisomers that could not hitherto be separated. In its NMR spectrum ($CDCl_3$) the methyl signals occur at 2.47 and 2.04 ppm (the latter is split, $^4J_{H,P}$ = 2 Hz, rel. areas 2:1).

Correct analytical data were obtained for all the products.

2-Oxo-2,3,3,4-tetraphenyl-1,2λ⁵-oxaphosphetan (5a') and 4-(α-naphthyl)-2-oxo-2,3,3-triphenyl-1,2λ⁵-oxaphosphetan (5b'):

30 mmol (9.54 g) of *(1a)* and 100 mmol of benzaldehyde or 1-naphthaldehyde in benzene (750 ml) were irradiated (Duran-50 filter, Philips HPK 125 W) until at least 50% of the theoretical amount of nitrogen was liberated. Evaporation, dissolution of the residue in methanol (50 ml) and crystallization at −20°C gave *(5a')* or *(5b')*. The filtrate was evaporated and the residue chromatographed in benzene (1000 ml) on Woelm silica gel (300 g, 0.05 to

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0.2 mm) to remove unchanged aldehyde. Further elution with ether (2500 ml) afforded 7-(*exo*-diphenylphosphoryl)-7-*endo*-phenylnorcaradiene.

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[1] Carbenes. Part 6. – Part 5: *H. Scherer, I. Hartmann, M. Regitz, B. D. Tunggal*, and *H. Günther*, Chem. Ber. *105*, 3357 (1972).

[2] *M. Regitz, A. Liedhegener, W. Anschütz*, and *H. Eckes*, Chem. Ber. *104*, 2177 (1971).

[3] *H. Günther, B. D. Tunggal, M. Regitz, H. Scherer*, and *T. Keller*, Angew. Chem. *83*, 585 (1971); Angew. Chem. internat. Edit. *10*, 563 (1971).

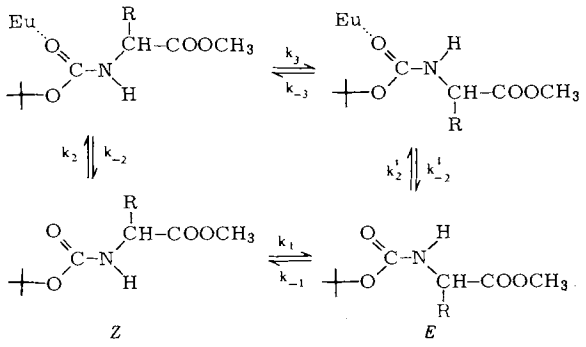
[4] All three fragments appear in the mass spectrum.

Dynamic NMR Measurements of Boc-amino Esters with Application of Lanthanoid Shift Reagents[1][**]

By *Horst Kessler* and *Michael Molter*[*]

Highly resolved NMR spectra are extremely well suited for demonstration of intramolecular mobility. The method fails, however, when the NMR spectra of the isomers do not differ sufficiently (accidental equivalence) and when the equilibrium lies greatly to one side. We have found that the use of lanthanoid shift reagents such as Eu(fod)$_3$ [tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octane-dionato)europium(III)] can lead to success in such cases.

The ^{1}H-NMR spectra of Boc-glycine methyl ester *(1)* and Boc-L-alanine methyl ester *(2)* in $CDCl_3$ at 90 MHz are independent of temperature and it is not possible to recognize any hindrance to rotation around the urethane N—C bond from these spectra. Nevertheless all the signals are doubled in the spectrum of *(1)* or *(2)* in $C_2D_2Cl_4$ at 0 °C after addition of Eu(fod)$_3$[2], showing the presence of the two rotamers side by side. The complexation occurs preferentially with the *E*-isomer that is present in smaller amounts. Its signals are more strongly shifted and become more intense as the concentration of Eu(fod)$_3$ is increased. Only if the molar ratio of Eu(fod)$_3$ to substrate approaches unity do the signals of the *Z*-isomer, now present in smaller amount, follow the same pattern.



(1), R = H; *(2)*, R = CH_3; *(3)*, R = CH_2-C_6H_5

Assignment of the rotamers is effected by comparing the lanthanoid-induced shifts Δ[4]. It can be assumed that complexation occurs at the urethane-carbonyl group. The signals of the *tert*-butyl group are thus relatively strongly shifted in both rotamers. Although the C_α-protons are further away from the europium ion in the *E*- than in the *Z*-conformation, the signal of the former is at first more shifted because of its greater complex formation. However, with increasing Eu(fod)$_3$ concentration [*e.g.*, for *(1)* > 38 mol-%] the strength of this signal is, as expected, overhauled by that of the *Z*-C_αH signal because of the increased complexation of the *Z*-form that now clearly occurs. If the shifts of the C_αH-protons are referred to those of the *tert*-butyl groups, the values shown in Table 1 are obtained, whence the assignments follow unambiguously. Extrapolation of the Eu(fod)$_3$ concentration to zero shows that the Boc-α-amino acids studied exist in $CDCl_3$ or $C_2D_2Cl_4$ preferentially in the *Z*-conformation, but the *E*-conformations are clearly better complexed so that their contribution increases with increasing Eu(fod)$_3$ concentration.

If the solution of *(1)* containing Eu(fod)$_3$ is warmed one observes coalescence of four groups of signals, corresponding to occurrence of rotation around the urethane bond. The chemical shifts $\Delta\nu$ (without exchange) in the low-temperature region are only slightly temperature-dependent, so they can be extrapolated without much difficulty. The free activation enthalpies of rotation around the urethane bond can be determined from the line broadenings in the usual way and are found to lie in the expected range (see Table 1)[1,5].

Table 1. Data for Boc-L-α-amino acid methyl esters calculated from the ^{1}H-NMR spectra of solutions in $C_2D_2Cl_4$ after addition of Eu(fod)$_3$.

	(1) Boc-Gly-OCH_3		*(2)* Boc-Ala-OCH_3		*(3)* Boc-Phe-OCH_3	
	Z	*E*	*Z*	*E*	*Z*	*E*
[mol-%] Eu(fod)$_3$ referred to the substrate	Proportions of the isomers at 7 °C [%]					
0	>88	<12	>92	<8	90 [a]	10 [a]
20	60	40	71	29	68	22
40	36	74	49	51	52	48
60	17	83	32	68	37	63
$\Delta_{C_\alpha H}/\Delta_{Boc}$ [b]	3.9	0.33	22	0.18	13	0.11
$\Delta G^{\neq}_{Z\to E}$ [kcal/mol] [c]	16.1 ± 1.0		15.4 ± 1.0		15.9 ± 1.0 [a]	

[a] In this compound the proportions of the two conformations can be recognized from the signal of the *tert*-butyl group even without addition of Eu(fod)$_3$. The other signals are not split.
[b] Ratio of the Eu(fod)$_3$-induced splitting at concentrations of Eu(fod)$_3$ up to 30 mol-% reffered to the substrate.
[c] Line widths evaluated at 32 °C; 34 mol-% of Eu(fod)$_3$ referred to the substrate.

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To interpret the barriers we can start with the fact that the equilibrium of complexation (k_2) is established rapidly on the NMR time scale. The process observed is thus, to a first approximation, the rotation (k_1) around the urethane bond in the uncomplexed molecule. However, the barrier observed can become somewhat greater as the $Eu(fod)_3$ concentration is increased, because the double-bond character of the C—N bond increases on complex formation.

Use of lanthanoid shift reagents thus broadens the field of application of dynamic NMR spectroscopy[6] in that small amounts of energetically unfavorable isomers can be recognized and the kinetics of the interconversion can be followed. A particular advantage is the ability to change considerably the isomeric ratios, but a prerequisite for this is that the energetically unfavorable isomer shall be better complexed than the isomer that is favored without addition of the shift reagent.

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[1] The Conformations of Protected Amino acids. Part 2.—Part 1: *M. Branik* and *H. Kessler*, Tetrahedron, in the press.

[2] $Eu(fod)_3$ leads to narrower lines than $Eu(dpm)_3$ [3], so that measurements can be made at lower temperatures.

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[6] It has been shown very recently for the case of dimethylformamide (see ref. [3]) that the isomeric ratio and the splitting $\Delta\nu$ (without exchange) can be changed by addition of lanthanoid shift reagents [7]. The examples described above are, to the best of our knowledge, the first determinations of previously unknown barriers to rotation.

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Synthesis of Valinomycin by the Phosphite Method[**]

By *Manfred Rothe* and *Wolfgang Kreiss*[*]

Dedicated to Professor Hans Brockmann on the occasion of his 70th Birthday

Valinomycin is a macrocyclic depsipeptide[1] built up of alternating amino and hydroxy acids, and having the structure cyclo(Val-D-Hyv-D-Val-Lac)$_3$[2]. Its antibiotic activity and ability to transport potassium ions through lipid membranes justify the development of efficient synthetic methods.

All previous methods of its preparation proceed through a linear dodecapeptide which is obtained by fragment condensation (classical and solid phase methods) and subsequent cyclization by the acid chloride method[3]. We have used the phosphite method for the ring closure[4] which was used previously by us for the synthesis of gramicidin S[5] and fungisporin[6].

As a further substantial simplification, the symmetrical structure permits direct synthesis from a tetradepsipeptide unit by cyclotrimerization. Moreover, the known[7] oligomeric cycloocta- and cyclohexadeca-peptide as well as the unknown first member of the polymer-homologous series, namely cyclo(Val-D-Hyv-D-Val-Lac) were obtained. All four cyclic compounds can be separated by gel chromatography (Sephadex LH 20/methanol) and characterized by mass and IR spectroscopy ($n=1-3$; cf. Table 2); the known compounds can also be characterized by comparison of m.p. and $[\alpha]_D$ data with values given in the literature.

Table 1. Cyclization of the tetradepsipeptide H(Val-D-Hyv-D-Val-Lac)OH.

Tetradepsipeptide c [mol/l]	Cyclodepsipeptide, yield [%] Tetra-	Octa-	Dodeca- (Valinomycin)
0.05	5	14	2
0.01	7	1	0.1

Cyclization experiments were carried out under various conditions with the sequences H(Val-D-Hyv-D-Val-Lac)$_n$OH having $n=1,2$ and 3. The products formed from the sequence with $n=1$ contained, besides the cyclotetradepsipeptide, the next two ring homologs with $n=2$ and 3 (including valinomycin). The linear octaptide gave the cycloocta- and cyclohexadecadepsipeptide, whereas on cyclization of the dodecapeptide ($n=3$) no cyclic product other than valinomycin was obtained. Yields and proportions of the cyclic oligomers depend greatly on the concentration of the linear peptide used and accord with the dilution principle (Table 1).

The highest yields of cyclodepsipeptide varied with the chain length of the linear depsipeptide used (Table 2), presumably for steric reasons.

Table 2. Dependence of the cyclization tendency on chain length.

n	H(Val-D-Hyv-D-Val-Lac)$_n$OH c [mol/l]	cyclo(Val-D-Hyv-D-Val-Lac)$_n$ Yield [%]
1	0.01	9
2	0.001	74
3	0.01	33

The results already obtained prove the suitability of the phosphite method for ring closure of depsipeptide sequences. Noteworthy are the rapid and simple procedure (batch method) and the easy working up. The reaction conditions (relatively high temperature, diethyl phosphite as solvent) indicate its use particularly for sparingly soluble sequences and for those where cyclization is sterically hindered.

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[2] Abbreviations: Val = L-valine, D-Val = D-valine, D-Hyv = D-α-hydroxyisovaleric acid, Lac = L-lactic acid.

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General procedure:

The linear depsipeptide is dissolved together with 2 equiv. of *o*-phenylene chlorophosphite in diethyl phosphite and heated under nitrogen at a bath temperature of 100 °C. For cyclization a solution of 3 equiv. of triethylamine dissolved in 10 ml of diethyl phosphite is added dropwise to the reaction mixture with vigorous stirring. The reaction mixture is stirred for 30 min at the above temperature, then cooled and evaporated under oil-pump vacuum. The oily residue is dissolved in methylene dichloride, extracted with 10% $NaHCO_3$ solution, and then with water. After evaporation, the residue is chromatographed on Sephadex LH 20 (eluant: methanol); the oligomeric cyclodepsipeptides are obtained from the fractionated eluates.

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Direct Synthesis and Separation of Asymmetric Phosphane-Manganese Complexes[1]

By *Henri Brunner* and *Wolfgang Rambold*[*]

The following optically active compounds have so far found application in the preparation of diastereoisomeric organometallic compounds of the transition elements: the mentholate ion $OC_{10}H_{19}^-$[2,3]; the isocyanide $C{\equiv}NCH(CH_3)(C_6H_5)$[3]; the amine $H_2NCH(CH_3)(C_6H_5)$[4]; and the chelate Schiff bases of 2-pyridinaldehyde and of the 2-pyrrolaldehyde anion with α-phenylethylamine[3]. Since phosphanes are excellent ligands in transition metal complexes of lower oxidation states, optically active phosphanes should be universally applicable for the direct introduction of diastereoisomerism.

The reaction of the secondary amine (*S*)-(−)-$(CH_3)HNCH(CH_3)(C_6H_5)$[5] [obtainable from (*S*)-(−)-$H_2NCH(CH_3)(C_6H_5)$] with diphenylchlorophosphane does not involve the center of asymmetry; the conveniently accessible potential ligand *(1)* is therefore optically pure.

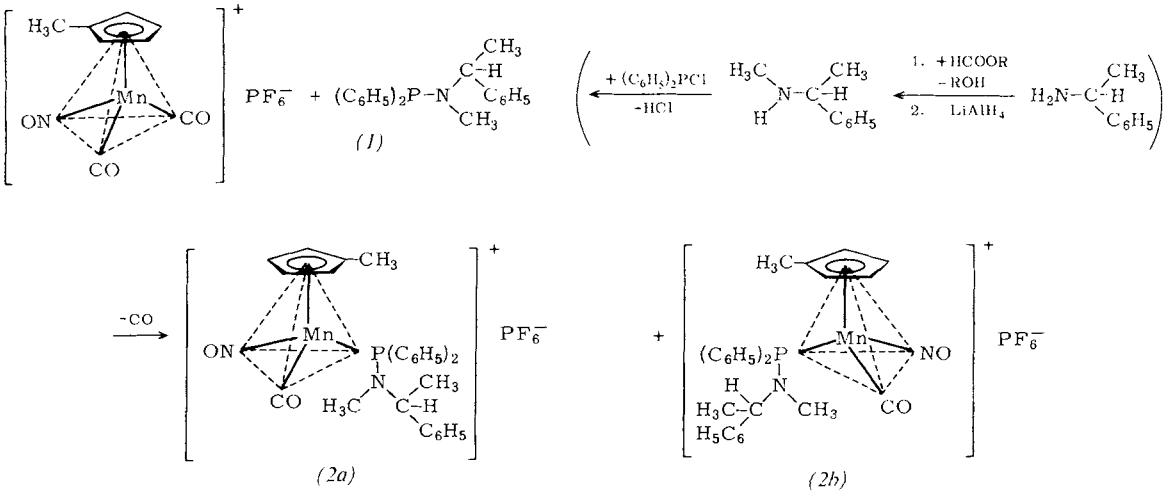
Reaction of $[C_5H_5Mn(CO)_2NO]^+PF_6^-$ with $P(C_6H_5)_3$ affords the monosubstitution product $[C_5H_5Mn(CO)(NO)P(C_6H_5)_3]^+PF_6^-$[6]. Correspondingly, *(1)* displaces one of the enantiotopic CO groups in $[CH_3C_5H_4Mn(CO)_2NO]^+PF_6^-$ (KBr: ν_{CO} 2150 and 2100 cm^{-1}; ν_{NO} 1860 cm^{-1}). There results a diastereoisomeric pair *(2a)/(2b)* which can be resolved owing to solubility differences. The optical purity of the fractions obtained in the individual separation steps can be established by NMR spectroscopy since the two diastereoisomers differ in their ^{1}H-NMR spectra.

(2a) and *(2b)* display identical IR spectra (KBr): ν_{CO} 2060 cm^{-1}; ν_{NO} 1795 cm^{-1}. Their specific rotations and ^{1}H-NMR parameters are listed in Table 1.

Like the enantiomers (+)- and (−)-$[C_5H_5Mn(CO)(NO)P(C_6H_5)_3]^+PF_6^-$, the optically active diastereoisomers *(2a)* and *(2b)* are configurationally stable[7]. The rotations of their solutions remain constant for a long period in the absence of light and oxygen.

Preparation of
(S)-(+)-(C_6H_5)PN$(CH_3)CH(CH_3)(C_6H_5)$ (1)

(*S*)-(−)-α-Phenylethylamine is at first formylated with $HCOOC_2H_5$ and then reduced with $LiAlH_4$ to give (*S*)-(−)-$(CH_3)NHCH(CH_3)(C_6H_5)$[5]: $[\alpha]_D^{25} = -82°$ (neat, $d^{25} = 0.92\,g\,cm^{-3}$). A solution of freshly distilled diphenylchlorophosphane (18.4 g, 0.08 mol) in ether (50 ml) is added dropwise to this amine (30 g, 0.22 mol) in diethyl ether (200 ml) at 0—5 °C over 2 h with exclusion of air and moisture. The reaction mixture is refluxed for 4 h, the solvent drawn off (after filtration to remove the amine hydrochloride), and the residue extracted with three 30-ml portions of pentane. After concentration of the pentane extract to 20 ml, residual hydrochloride is removed first at −20 °C and the solvent and excess amine are then removed in a high vacuum. Yield of *(1)* 93%; mass spectrum: molecular ion *m/e* 319, rel. int. 72% (based on *m/e* 262, rel. int. 100%).



Preparation of the diastereoisomeric complex salts (2a) and (2b)

$[CH_3C_5H_4Mn(CO)_2(NO)]^+PF_6^-$ (1.57 g, 4.3 mmol) in acetone (50 ml) is united with *(1)* (1.38 g, 4.3 mmol) in acetone (20 ml) at room temperature with exclusion of air (vigorous liberation of CO). After 4 h the solution is filtered and the solvent drawn off. The residue is chromatographed in CH_2Cl_2 (5 ml) over Sephadex LH 20/CH_2Cl_2. Removal of the CH_2Cl_2 leaves an oily residue which can be converted into powder form by prolonged stirring in pentane. Only

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Table 1. Specific rotations and ^{1}H-NMR data of *(1)*, *(2a)*, and *(2b)*.

	(1)	*(2a)*	*(2b)*
specific rotations	(*ca.* 15 mg/ml, CH_2Cl_2)	(*ca.* 4 mg/ml, CH_2Cl_2; 100% opt. pure)	(*ca.* 4 mg/ml, CH_2Cl_2; 70% opt. pure)
	$[\alpha]_{589}^{25} = +57$	+256	−162
	$[\alpha]_{579}^{25} = +64$	+307	−208
	$[\alpha]_{546}^{25} = +72$	+495	−315
	$[\alpha]_{436}^{25} = +156$	−1470	+806
	$[\alpha]_{365}^{25} = +340$		
^{1}H-NMR	(C_2Cl_4; T60)	([D_6]acetone; XL100)	([D_6]acetone; XL100)
	[a] assignment	[a] assignment	[a] assignment
	^{2}8.47(3); 8 [b] C—CH_3	^{2}8.36(3); 7 [b] C—CH_3	^{2}8.40(3); 7 [b] C—CH_3
	^{2}7.82(3); 3 [d] N—CH_3	^{m}7.90(3); [c] C_5H_4—CH_3	^{m}7.90(3); [c] C_5H_4—CH_3
	^{m}5.40(1); 8 [b] C—H	^{2}7.46(3); 9 [d] N—CH_3	^{2}7.48(3); 9 [d] N—CH_3
	^{m}2.77(15); C—C_6H_5, $P(C_6H_5)_2$	^{m}5.17(1); C—H	^{m}5.17(1); C—H
		^{m}5.01, ^{m}4.70, ^{m}4.37 (4); C_5H_4	^{m}5.01, ^{m}4.70, ^{m}4.37 (4); C_5H_4
		^{1}2.64(5); C—C_6H_5	^{1}2.60(5); C—C_6H_5
		^{m}2.31(10); $P(C_6H_5)_2$	^{m}2.31(10); $P(C_6H_5)_2$

[a] τ-values (rel. int.) TMS internal standard; coupling constants [Hz] – multiplicities: superscripts preceding the τ-values.
[b] J_{CH-CH_3}. [c] Beneath acetone signal. [d] J_{PNCH_3}.

part of the yellow salt dissolves in a 30-ml portion of methanol. The more sparingly soluble fraction is dissolved in acetone and cooled to −20 °C with addition of ether (until crystallization starts). This separating operation is repeated with the resulting recrystallized product to give the less soluble (+)-rotatory diastereoisomer *(2a)* in optically pure (^{1}H-NMR) form; yield *ca.* 10%; dec. 145 °C. The methanolic solution obtained in the first fractionation is evaporated down to a volume of 3 ml and allowed to crystallize at −20 °C. After repetition of this separating step the residual solution contains the more readily soluble (−)-rotatory diastereoisomer *(2b)*, contaminated, according to the ^{1}H-NMR spectrum, with about 15% of *(2a)*; yield *ca.* 15%, dec. 130 °C.

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[1] Optically Active Transition Metal Complexes, Part 23. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.—Part 22: *H. Brunner* and *W. A. Herrmann*, Z. Naturforsch. in press.

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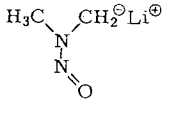
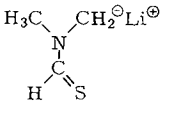
Nucleophilic Thioacylation with Solutions of Dimethylthiocarbamoyllithium[**]

By *Dieter Enders* and *Dieter Seebach*[*]

Methods for nucleophilic acylation[1] have recently found increasing application in organic synthesis[2]. In connection with our studies on nucleophilic aminoalkylation with metalated nitrosamines[3] such as *(1)* we have sought other "activating" groups and checked the possibility of preparing the lithium derivative *(2)* from dimethylthioformamide[4]. Much to our surprise a yellow solution of dimethylthiocarbamoyllithium *(3)*[5] is formed in almost quantitative yield (according to deuterolysis) on adding thioformamide to the THF solution of lithium diisopropylamide at −100 °C. Addition of benzophenone leads to the adduct *(4a)* in 85% yield (see experimental section and Table 1).



(1)



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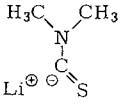

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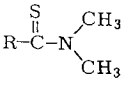

(4)

If the reaction mixture is allowed to warm to −78 °C within 15 min after the metalation and then stirred for a further 15 min period at this temperature, only 20% of *(4a)* is obtained. As shown in Table 1 other aliphatic and aromatic aldehydes and ketones can be converted into α-hydroxythioamides in good yields. Reaction with methyl iodide leads to *(4h)*, and with methyl benzoate to *(4g)* (Table 1).

Experimental:

N,N-Dimethyl-2-hydroxy-2,2-diphenylthioacetamide (4a)

To a stirred solution of lithium diisopropylamide (10 mmol) in THF/hexane (5:1) is added a solution of *N,N*-dimethylthioformamide (0.88 g, 10 mmol) in THF (2 ml) over 1 min at −100 °C. After 3 min the resultant yellow solution is treated with a solution of benzophenone (1.82 g, 10 mmol) in THF (7 ml). The bath temperature is allowed to rise to −70 °C over a period of 1 h and the reaction mixture then neutralized with glacial acetic acid (0.6 ml). Work-up

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Table 1. *N,N*-Dimethylthioamides, R—CS—$N(CH_3)_2$ *(4)* synthesized.

	R	Yield [%]	M.p. [°C] B.p. [°C/torr] [a]	IR [cm^{-1}] [b, c]	NMR [b], δ (in CCl_4 or $CDCl_3$)
(4a)	$(C_6H_5)_2C(OH)$	85	134	1525 [d]	2.67 (s, 3H), 3.48 (s, 3H), 6.43 (s, 1H), 7.24 (s, 10H)
(4b)	$C_6H_5C(CH_3)(OH)$	65	66.5	1515 [e]	1.78 (s, 3H), 2.85 (br.s, 3H), 3.42 (br.s, 3H), 5.44 (br.s, 1H), 7.25 (m, 5H)
(4c)	$C_6H_5CH(OH)$	75	100	1540 [d]	3.05 (s, 3H), 3.45 (s, 3H), 5.15 (s, 1H), 5.19 (s, 1H), 7.26 (m, 5H)
(4d)	$(CH_3)_2C(OH)$	85	80/0.03	1520 [f]	1.50 (s, 6H), 3.45 (s, 6H), 4.77 (br.s, 1H)
(4e)	$C_2H_5CH(OH)$	80	80/0.01	1530 [f]	0,8–1.80 (m, 5H), 3.27 (s, 3H), 3.42 (s, 3H), 3.90 (br.s, 1H), 4.20 (m, 1H)
(4f)	1-Hydroxycyclohexyl	65	98.5	1510 [d]	1.0–2.25 (m, 10H), 3.50 (s, 6H), 4.10 (s, 1H)
(4g)	C_6H_5CO	85	83	1540 [d]	3.14 (s, 3H), 3.46 (s, 3H), 7.40 (m, 3H), 7.84 (m, 2H)
(4h)	CH_3	50	72.5 [g]	1515 [e]	2.55 (s, 3H), 3.31 (s, 3H), 3.40 (s, 3H)

[a] Oil-bath temperature in molecular distillation.
[b] IR spectra: Perkin-Elmer-225 Grating Spectrometer; NMR spectra: JEOL-Minimar-100 Spectrometer.
[c] For the absorption of thioamides a typical range of 1500—1550 cm^{-1} is quoted [6].
[d] In KI.
[e] In KBr.
[f] Without solvent.
[g] Ref. [7]: 73—74°C.

with methylene dichloride as solvent affords a viscous oil that gradually crystallizes. After washing with pentane, dissolution in chloroform, and subsequent precipitation with ether/pentane *(4a)* crystallizes as colorless leaflets in 85% yield (2.3 g).

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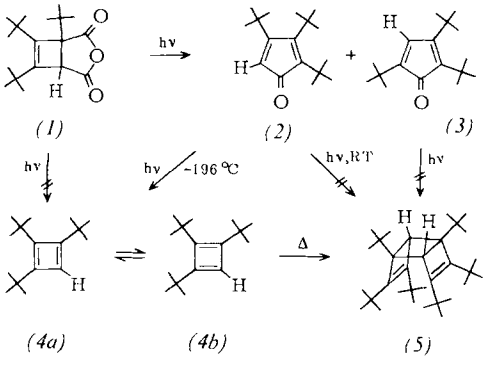
Tri-*tert*-butylcyclobutadiene[1][**]

By *Günther Maier* and *Arnaldo Alzérreca*[*]

Dedicated to Professor Heinrich Hellmann on the occasion of his 60th Birthday

The predicted antiaromaticity of cyclobutadiene requires great reactivity, particularly towards dimerization. By introduction of sterically demanding groups it should be possible to prolong the lifetime of this molecule without disturbing the electronic character of the ring system. That this concept is correct is shown by the fact that the considerable reactivity of unsubstituted[2] and of mono-*tert*-butylcyclobutadiene[2] decreases in 1,2-di-*tert*-butyl-[3,4] and still further in 1,3-di-*tert*-butyl-cyclobutadiene[4]. Tri-*tert*-butylcyclobutadiene *(4)* might thus be able to exist as the monomer at room temperature—a suggestion that has now been proven by experiment.

Irradiation of the anhydride *(1)*[4] at room temperature leads to the cyclopentadienones *(2)* and *(3)*. As a result of an observation that the carbonyl bands of the dienones become less intense on prolonged irradiation of *(1)* in a matrix at −196°C, we have investigated their photochemical behavior further and have found that *(3)* is photostable at all temperature regions but *(2)* only at room temperature. Irradiation of *(2)* at −196°C induces elimination of carbon monoxide. The CO can be detected by IR spectroscopy, but the structure of the resulting hydrocarbon follows from the result of preparative irradiation of *(2)* in a matrix of Rigisolve[***] at −196°C: if the solution obtained on thawing is kept for a day at room temperature, the dimer *(5)* {m.p. 126—127°C; MS: $m/e = 440$ (M^+); correct elemental analyses[5]} of tri-*tert*-butylcyclobutadiene *(4)* can be isolated in 82% yield.



On irradiation for 3 h at −196°C in a glass of perdeuteriated methylcyclohexane (sealed quartz NMR tube), *(2)* is converted almost completely into a new species that is relatively stable even after warmup to room temperature and is characterized by three signals in the 100 MHz ^{1}H-NMR spectrum [$\tau = 4.65$ (1 H), 8.86 (9 H) and 8.95

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[***] Rigisolve (Merck): 2,2-dimethylbutane/*n*-pentane (8:3).

(18 H)]. If this product is kept for a day at room temperature, only the spectrum of the dimer *(5)* [$\tau = 7.55$ (2 H), 8.58 (18 H), 8.79 (18 H) and 8.86 (18 H)] is recorded. It must be concluded, therefore that the intermediate is tri-*tert*-butylcyclobutadiene *(4)*.

Thus, for the first time, a cyclobutadiene has been produced that is stable at room temperature but is substituted only by alkyl groups and must therefore contain an essentially genuine π-electron system[6].

Tri-*tert*-butylcyclobutadiene *(4)*[10] is extremely sensitive to oxygen: on admission of air autoxidation is faster than dimerization.

The chemical shift of the isolated proton ($\tau = 4.65$) lies appreciably higher than that of the ring protons in 1,2,3,5-tetra-*tert*-butylbenzene (3.07[11]). It is remarkable[12, 13] that the external protons of [16]annulene (4.67[14]) and 1,7-methanol[12]annulene (4.2—4.6[15]) have almost the same chemical shift as the isolated proton in *(4)*. Consequently the NMR spectrum of *(4)* can be considered as an indication for a paramagnetic ring current (antiaromatic character) comparably strong as in the higher planar [4*n*]annulenes.

The fact that both the *tert*-butyl groups next to the hydrogen atom appear as one signal in the NMR spectrum of *(4)* can have one of two causes: either *(4)* has a square structure and a triplet ground state, or it exists as a singlet molecule with alternating bond lengths and the NMR spectrum is the result of a rapid valence isomerization *(4a)*$\rightleftharpoons$*(4b)*. We favor the second alternative, not least because of the electron spectrum of *(4)*, which has no well-developed band above 300 nm, in agreement with the predicition for a singlet cyclobutadiene that departs from D_{4h} symmetry[16].

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[5] In analogy to many other examples (*G. Maier*, Angew. Chem., in the press) the *syn*-configuration is assumed for *(5)*.

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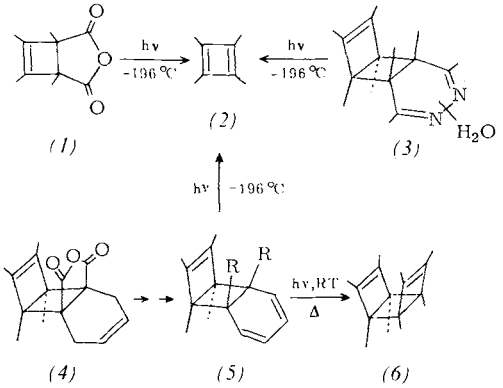
Tetramethylcyclobutadiene, an Excellent Donor Molecule[1][**]

By *Günther Maier, Wolfram Mayer, Claus Haacke*, and *Rainer Askani*[*]

Dedicated to Professor Heinrich Hellmann on the occasion of his 60th Birthday

Tetramethylcyclobutadiene *(2)* can be prepared photochemically by removal of the anhydride grouping from *(1)*[2] or of tetramethylpyridazine from *(3)*[3]. UV-spectroscopic detection of the cyclobutadiene *(2)* frozen in a matrix at -196 °C after low-temperature photofragmentation of *(1)* is difficult because of the tetramethylcyclopentadienone that is also present[4]. On the other hand it appears reasonable to assign to the cyclobutadiene *(2)* the maximum observed on matrix-irradiation of *(3)*. Yet it remains uncertain how far charge-transfer interaction between *(2)* and tetramethylpyridazine might falsify the picture.

To obtain answers to these problems, we have sought further photoprecursors of *(2)* and have applied to the compounds *(5a)*—*(5d)* the principle used with *(3)*, namely to force formation of the cyclobutadienes by removing a component stabilized by delocalization.



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

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

(5a), R-R = -CO-O-CO- *(5c)*, R = CO_2CH_3

(5b), R-R = $-CH_2-O-CH_2-$ *(5d)*, R = CH_2OH

The anhydride *(4)* is available for preparation of *(5a)*—*(5d)*; it is readily accessible by treatment of 1,4-cyclohexadiene-1,2-dicarboxylic anhydride with 3,4-diiodo-1,2,3,4-tetramethylcyclobutene in the presence of mercury. Addition of bromine and double elimination of HBr with 1,8-diazabicyclo[5.4.0]undec-7-ene affords the anhydride *(5a)* (m.p. 112—114 °C). The action of CH_2N_2 on *(5a)* in CH_3OH leads to the diester *(5c)* (m.p. 110 °C), reduction by $LiAlH_4$ yields the alcohol *(5d)* (m.p. 165 °C); and the ether *(5b)* (m.p. 124—125 °C) is formed on reaction of *(5d)* with 1 mol of *p*-toluenesulfonyl chloride.

The structures of *(5a)*—*(5d)* are proved by their spectral data. The mass spectra show that the cyclobutadiene ring is easily split off. *(5c)* and *(5d)* contain, contrary to expectation[5], an intact bicyclo[4.2.0]octadiene ring ske-

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leton although there is no additional five-membered ring to act as anchor[6].

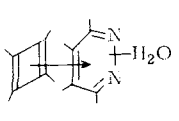
Irradiation (Hg low-pressure lamp, Vycor) of the photoprecursors *(5)* at room temperature leads to smooth cleavage in the desired manner. Products are the *syn*-tricycle *(6)* and the corresponding benzene derivative. Photofragmentation (Hg high-pressure lamp, Solidex) in acetone proved particularly suitable. Sensitized and direct irradiation of *(5a)* to *(5d)* give the same products. By way of contrast, the heterocycle yields exclusively octamethylcyclooctatetraene in place of *(6)* on sensitization by benzophenone[7].

(5a) to *(5d)* are readily split to tetramethylcyclobutadiene *(2)* and the aromatic component even on matrix irradiation (Hg low-pressure lamp, Vycor) at −196 °C. After thawing, again only the tricycle *(6)* and the appropriate benzene derivative can be detected, along with very small amounts of octamethylcyclooctatetraene.

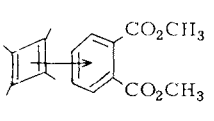
Accordingly, the same UV maximum should appear on low temperature fission of *(5a)*—*(5d)* and of *(3)*. The experimental result is, however, completely different: on irradiation of the anhydride *(5a)* the matrix becomes red (ether, pentane, tetrahydrofuran; $\lambda_{max} = 495$ nm), with the diester *(5c)* yellow (tetrahydro-2-methylfuran; $\lambda_{max} = 385$ nm), but with *(5b)* (Rigisolve) and *(5d)* (tetrahydro-2-methylfuran) the matrix remains colorless.

This means that a different UV spectrum is obtained by starting from each of six precursors although it is certain that in each case the same species, namely tetramethylcyclobutadiene, is present in the matrix. Our explanation for these contradictory results is as follows: if the photofission produces an acceptor molecule alongside the extremely good electron donor *(2)*, then a charge-transfer complex can be formed in the matrix. The necessary geometrical arrangement is already prescribed by the starting materials *(3)* and *(5)*. This possibility does not exist with the anhydride *(1)*.

Hence: The maximum at 423 nm (tetrahydro-2-methylfuran) observed on cleavage of *(1)* arises from tetramethylcyclopentadienone; the band at 375 nm (ether, isopentane, ethanol) in the case of *(3)* has its origin in formation of the charge-transfer complex *(7)*; this interaction is better developed in the complex *(8)* and still more so in *(9)*; the absorption band is shifted to 385 and 495 nm, respectively, owing to the better acceptor properties of dimethyl phthalate and phthalic anhydride. Only on fragmentation of *(5b)* and *(5d)* "free" tetramethylcyclobutadiene *(2)* is formed—phthalan and 1,2-phenylenedimethanol do not act as acceptors. Thus, like tri-*tert*-butylcyclobutadiene[8], uncomplexed *(2)* shows no absorption band above 300 nm.



(7)



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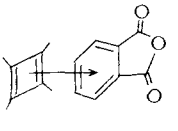

(9)

This result is in agreement with the prediction[9] for a rectangular singlet cyclobutadiene, which should have no allowed transition above a band at 198 nm, whereas a maximum at 380 nm is calculated for square triplet cyclobutadiene. Unsubstituted[10,11] and mono-*tert*-butyl-cyclobutadiene[10] are characterized by an absorption band at 305 nm. Further experiments are necessary to decide whether UV spectra may in fact be used in drawing such conclusions and whether a multiplicity exchange occurs depending on the number of substituents.

It is important in this connection that *(5a)*, *(5c)*, and *(5d)* can be split also thermally to yield tetramethylcyclobutadiene *(2)*, again with formation of *(6)*. The anhydride *(5a)* fragments even at room temperature, although then very slowly[12]; this offers the possibility of using pyrolysis to obtain information about the properties of tetramethylcyclobutadiene also at high temperatures.

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ESCA Studies on N_2-, N_2H_2-, N_2H_4- and NH_3-Complexes of Manganese[**]

By *Herbert Binder* and *Dieter Sellmann*[*]

In the recently described series of manganese complexes $[C_5H_5Mn(CO)_2]_xL$ with $L = N_2$, N_2H_2, N_2H_4, NH_3, and $x = 1$ or 2 (for N_2H_2), we have, for the first time, species in which all possible reduction states of the N_2 molecule during nitrogen assimilation are bound to one and the same metal[1]. Their investigation by X-ray photoelectron (ESCA) spectroscopy ought to give an indication as to whether the formal oxidation numbers of the nitrogen in this series can be also confirmed physically, as well as providing further information about the electronic structure of the individual complexes.

Contrary to expectation the N1s binding energies of the N atoms bound directly to the metal do not reveal a regular progression on going to more negative oxidation numbers; this is even less so in the case of the Mn- and

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C1s-binding energies (Table 1). Hence no strict physical significance can be attached to the formal character of the oxidation number. The results do indicate, however, that the Mn—N bonds in all complexes have about the same polarity. The N1s energy differences (Mn—N) can be ascribed to two causes: on the one hand, due to different bond orders and electronenegativities, the atoms or groups of atoms attached to these N atoms influence the effective charge—here, the different number of H atoms should be especially mentioned; on the other hand, the Mn—N bond in the various complexes has undoubtedly different σ-π character.

other hand, the N1s binding energy of the NH_3 ligand is higher by about 0.1 eV; that is, complexation effects a reversal of the N1s binding energy ratio since the N_2 molecule is rendered considerably more negative than the NH_3 molecule. This is in agreement with the generally accepted assumption that N_2 functions as a σ-π ligand, NH_3, however, as a pure σ ligand.

$$\overset{\ominus}{Mn}-\overset{\oplus}{N}\equiv N \longleftrightarrow Mn=\overset{\oplus}{N}=\overset{\ominus}{N} \qquad \overset{\ominus}{Mn}-\overset{\oplus}{N}H_3$$

(1a) *(1b)* *(2)*

Table 1. Binding energies [eV] relative to C1s (286.6 eV) of the C_5H_5 ligands and charges on the nitrogen atoms [a].

Compound	Oxidation number of the N-Atom (N—Mn)	N1s	$Mn2p_{3/2}$	Mn3s	C1s (CO)	q_p
$C_5H_5Mn(CO)_3$	—	—	642.1	86.7	288.6	—
$C_5H_5Mn(CO)_2N_2$	0	403.0; 401.8	641.8	85.9	288.9	+0.36; +0.16
$[C_5H_5Mn(CO)_2]_2N_2H_2$	−1	403.6	642.2	86.8	288.2	+0.47
$C_5H_5Mn(CO)_2N_2H_4$	−2	402.7; 401.7	641.8	85.9	288.1	+0.31; +0.14
$C_5H_5Mn(CO)_2NH_3$	−3	403.1	641.7	85.8	290.0	+0.39

[a] The charges were determined from the correlation diagram given in Ref. [3].

The doublet structure of the N1s spectrum (Fig. 1a) of the N_2 complex is a direct indication of terminal bonding of the N_2 molecule to the Mn atom; since, according to chemical findings, the second N atom exhibits Lewis basicity and must therefore be negatively polarized it is very likely represented by the lower binding energy peak at 401.8 eV. ESCA studies on different N_2 complexes[2] also reveal "end-on" bonding and greater negative charge on the terminal N atom. According to *Nordberg et al.*[3] the N1s binding energy varies almost linearly with the charge (calculated on the basis of Pauling electronegativities), 5 eV corresponding to one atomic unit of charge. Accordingly, the difference of 1.2 eV between the two N1s lines in the N_2 complex corresponds to a charge separation of 0.24 atomic charge units. The N1s spectrum of the N_2H_4 complex (Fig. 1b) shows only one broad band, which originates from an unresolved doublet (distance between components, according to a computer analysis *ca.* 1.0 eV).

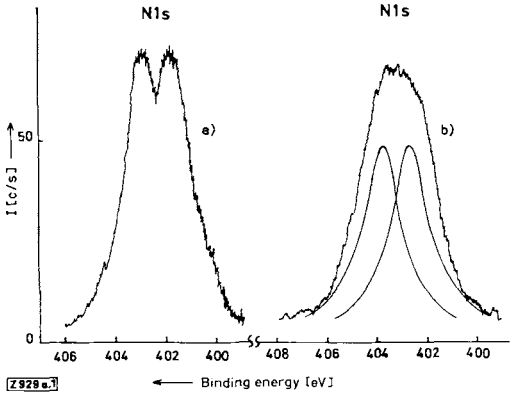

Fig. 1. ESCA spectrum of the 1s electrons of the nitrogen in a) $C_5H_5Mn(CO)_2N_2$, b) $C_5H_5Mn(CO)_2N_2H_4$.

Of special interest are the electronic changes which such different molecules as N_2 and NH_3 experience during complexation with a metal. In the gaseous phase N_2 has a binding energy about 4.3 eV higher than that of NH_3[4]. After addition to the $C_5H_5Mn(CO)_2$-fragment, on the

This also explains why a larger formal charge separation is observed for the N atom in $C_5H_5Mn(CO)_2N_2$ than in $C_5H_5Mn(CO)_2N_2H_4$. In contrast to the terminal N atom of the N_2H_4 complex, that in the N_2 complex can accept a negative charge, thus leading to increased polarity of the N—N bond. As in the case of the N_2 complex, ligand-metal σ-π interactions can be assumed to take place also in the N_2H_2 complex.

$$\overset{\ominus}{Mn}-\overset{\oplus}{N}H=\overset{\oplus}{N}H-\overset{\ominus}{Mn} \longleftrightarrow Mn=\overset{\oplus}{N}H-NH-\overset{\ominus}{Mn} \longleftrightarrow \overset{\ominus}{Mn}-NH-\overset{\oplus}{N}H=Mn$$

(3a) *(3b)* *(3c)*

Vibrational and ^{1}H-NMR spectroscopic findings would indicate the contributing form *(3a)* to be the most important form; this would also explain the relatively high N1s binding energy of 403.6 eV.

The binding energies of the $Mn2p_{3/2}$ levels are almost the same in all the complexes (Table 1), thus indicating that the charges on the manganese are roughly equal and that "long range" effects by the next but one neighboring atoms can be ruled out. Remarkably, however, the $Mn2p_{3/2}$ energy in $C_5H_5Mn(CO)_3$ decreases by 0.3 eV on substitution of a CO by the N_2 ligand. It can be concluded, therefore, that the total electron density of the Mn atom is greater in $C_5H_5Mn(CO)_2N_2$ than in $C_5H_5Mn(CO)_3$.

Experimental:

The X-ray photoelectronic spectra were recorded with a AEI-ES-100 spectrometer [photoionization with Al-$K\alpha_{1,2}$ (1486.6 eV)]. In order to avoid charge effects the compounds were sublimed at 20 °C as a thin film onto a cooled sample holder.

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cis-Diiminebis(pentacarbonyltungsten)[1]

By *Dieter Sellmann, Alfred Brandl*, and *Ralf Endell*[*]

Diimine, H—N=N—H, in complexed form is being discussed as an intermediate in N_2-assimilation[2]. The only transition metal complexes of diimine known to date are those with manganese and with chromium[1,3]. In an attempt to prepare the corresponding complex with tungsten by an analogous route we have found that the hydrazine complexes of chromium and tungsten employed as starting materials exhibit surprisingly different reactivities. Even more striking is the influence of the central metal atom in the comparable N_2H_4- and N_2H_2-bridged complexes of molybdenum: They are obviously so labile that until now only their intermediate existence has been observed. The different reactivities of Cr, Mo, and W complexes may reflect why molybdenum functions as an active center in nitrogenases. The analogous reaction for the synthesis[1] of $N_2H_2[Cr(CO)_5]_2$ *(1)*

$$\underset{(2)}{N_2H_4[W(CO)_5]_2} + H_2O_2 \xrightarrow[Na_2SO_4/-20\,^\circ C]{THF/HCl/Cu^{2+}} \underset{(3)}{N_2H_2[W(CO)_5]_2} + 2H_2O \quad (1)$$

led to a red coloring of the previously yellow reaction solution; thus indicating the formation of *(3)*. However, the desired tungsten complex could not be isolated. Only on using a tenfold excess of H_2O_2 could a very small quantity of *(3)* (<1%) be extracted from the insoluble reaction products.

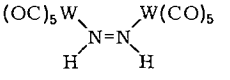
The oxidative formation of binuclear diimine from mononuclear hydrazine complexes, *e.g.* in the case of $N_2H_2[C_5H_5Mn(CO)_2]_2$ *(4)*, involves the occurrence of several reactive intermediates, which accounts for the very low yield of end product[3]. It is surprising, therefore, to find that a much better method for the preparation of *(3)* lies in the oxidation of the mononuclear hydrazine complex *(5)*:

$$\underset{(5)}{(OC)_5W{-}N_2H_4} + H_2O_2 \xrightarrow[Na_2SO_4/0\,^\circ C]{THF/Cu^{2+}} (3) + (2) + \text{decomposition products} \quad (2)$$

The compound *(3)* (black crystals after recrystallization from dark red-violet solutions in THF) decomposes in a sealed tube at 142—145 °C to give, *inter alia*, $W(CO)_6$. Even more surprising than the synthesis according to eq. (2), however, is the finding that *(3)* is obtained in the *cis*-form. Steric considerations, as well as the synthesis of *(4)*, would lead one to expect the *trans*-form. The *cis* structure of *(3)* is deduced from the IR spectrum (KBr), which shows five medium strong bands in the range 4000 to 600 cm^{-1}, very clearly separated from the typical absorptions of the $W(CO)_5$ groups. The five bands are characteristic for the *cis*-N_2H_2 ligand: 3450, 3250 (ν_{as} and ν_sNH), 1385 (νN=N), 1355 and 1085 cm^{-1} (δ_{as} and δ_sH—N—N—H). The shift of 30 cm^{-1} of the ν(N=N) vibration to lower frequencies compared to *(1)* points to a certain coupling with the νM—N vibration.

The ^{1}H-NMR spectrum ([D_6]-acetone, 26 °C) shows only a single peak at 16.38 ppm (referred to TMS), whose large shift is typical for protons of complexed diimine. The acidity derived therefrom is shown also in the H-D exchange with CD_3OD, which proceeds much more rapidly than in *(2)* or $(CO)_5WNH_3$.

IR, ^{1}H-NMR, and mass spectra, and the results of an elemental analysis lead us to propose the following structure, *i.e. cis*-diiminebis(pentacarbonyltungsten) for *(3)*.



UV-irradiation of a THF solution at −78 °C converts *(3)* into a dark blue compound, the color of which remains unchanged during evaporation of the solvent. The blue product is extremely thermolabile and is reconverted at −40 °C, both in the solid state as well as in solution, into the starting product *(3)*. Further investigations should clarify whether this blue substance is *trans*-*(3)* or perhaps the nitrene complex $(CO)_5WNH$ *(7)*.

Procedure:

All operations are carried out under nitrogen in anhydrous solvents.

0.75 g (2.1 mmol) of *(5)* is dissolved in THF (3 ml) in a Schlenk tube, cooled to −78 °C and stirred under addition of 4 g of Na_2SO_4, 0.05 ml of 0.1 N $CuSO_4$—H_2O solution, and 0.1 ml of H_2O_2 (70%) in 0.5 ml of THF. The highly viscous pulp is allowed to warm to 0 °C. After about 10 seconds the reaction starts and the yellow suspension changes color to red; after a further 10 seconds evolution of gas begins. After a total period of 5 minutes and evolution of *ca.* 140 ml of gas the reaction comes to a standstill. The solvent is evaporated at −20 °C; the black-brown residue is dried for 8 hours between −20° and +10 C in a high vacuum and then extracted four times with 10 ml of THF. The combined extracts are filtered at −20 °C and cooled down to −78 °C for 2 hours. Approximately 100 mg of crude *(3)*, contaminated with *(2)*, is precipitated. Twofold recrystallization from 5 ml of THF at −78 C affords pure *(3)*. Yield about 80 mg.

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[2] Cf. *J. R. Postgate*: The Chemistry and Biochemistry of Nitrogen Fixation. Plenum Press, London 1971.

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Structure of Diimine: IR Spectra of N_2H_2-, N_2D_2-, and $^{15}N_2H_2[Cr(CO)_5]_2$[1]

By *Dieter Sellmann, Alfred Brandl*, and *Ralf Endell*[*]

Such contradictory spectroscopic reports have seldom been made for a molecule as for diimine, HN=NH *(1)*. The

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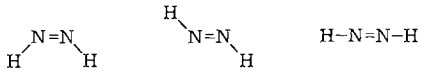
published studies on *(1)* are all characterized by the following features: 1) the samples contained large proportions of contaminants, *e. g.* up to 80% of NH_3; 2) the IR spectra were so poorly reproducible that agreement could not be reached even about the strong bands; 3) the theoretically required number of absorptions has never been found in the IR or UV spectra of *(1)*. Thus it is hardly surprising that the *cis* structure *(1a)*[2], the *trans* structure *(1b)*[3], and even mixtures of both[4] have all been deduced from the existing spectroscopic data. Other structures, such as *(1c)*, were ruled out only for chemical reasons; in no case has an unambiguous assignment of all the vibrational frequencies of *(1)* been possible.

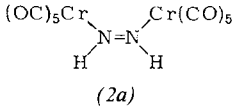


(1a) *(1b)* *(1c)*

However, unequivocal statements concerning the vibrational frequencies and the structure of *(1)* become possible with the IR spectra of the μ-diimine complexes $N_2H_2[Cr(CO)_5]_2$ *(2)*, $N_2D_2[Cr(CO)_5]_2$ *(3)*, and $^{15}N_2H_2[Cr(CO)_5]_2$ *(4)*. Complex *(3)* is obtained from *(2)* by H/D exchange with CH_3OD, while *(4)* is prepared by the same method as *(2)*[5] but with ^{15}N-labeled N_2H_4. H/D exchange with *(2)* and *(3)* proceeds so rapidly that protons are repeatedly reintroduced into pure *(3)*.

The characteristic absorptions of the $Cr(CO)_5$ groups, whose assignment is established by comparison with other compounds, appear in *(2)*, *(3)*, and *(4)* at the same frequencies. Their number, position, and intensity in the solid and in THF solution (νCO: 2055 w, 1950 vs, 1923 s cm^{-1}) indicate an almost undistorted C_{4v} symmetry of the $Cr(CO)_5$ groups and justify the assumption of local symmetry for the N_2H_2 ligands too. $Cr(CO)_5$ groups show no (typical) absorptions between 4000 and 2100, and 1800 and 700 cm^{-1} respectively; for this reason alone the bands appearing in these regions can be attributed to the diimine ligands. This assignment is supported by the spectra of the isotopically labeled compounds.

Since the selection rules require that 5, 3, and 2 normal modes of *(1a)*, *(1b)*, and *(1c)*, respectively, be IR active, the number of bands observed indicate that *(1)* has the *cis* form *(1c)* in the complex *(2)*. Particularly characteristic of *(1a)* is the occurrence of an N=N stretching vibration which is IR inactive in *(1b)* and *(1c)*. This constitutes the first spectroscopic proof for diimine in the *cis* form, corresponding to the proposed structure *(2a)* for the complex *(2)*.



(2a)

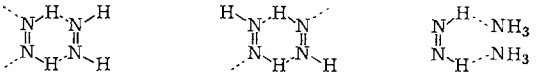
The frequencies observed[7] for the diimine ligands in *(2)*, *(3)*, and *(4)* are listed in Table 1.

Thus, contrary to previous observations[2-4], the NH stretching vibrations have values to be expected for NH compounds, and particularly for those in which the N atom participates in multiple bonds. Surprisingly, the isotopic shifts agree fairly accurately with the values calculated for free diimine; nevertheless, the N=N and Cr—N stretching vibrations are probably coupled, since the (N=N) vibration in $N_2H_2[W(CO)_5]_2$ *(5)*, an analog of *(2)*, is observed at 1385 cm^{-1}. The other N_2H_2 vibrations, however, display a remarkable lack of sensitivity to changes of the central metal and display practically the same frequency in *(2)* as in *(5)*; they thus represent almost pure diimine vibrations.

Table 1. IR frequencies (KBr; cm^{-1}) of the diimine ligands in the complexes *(2)*, *(3)*, and *(4)*.

N_2H_2	N_2D_2	$^{15}N_2H_2$	Assignment
3480	2445	3435	ν_{as}(NX)
3250	2380	3250	ν_s(NX)
1415	1415	1370	ν(N=N)
1352	998	1350	δ_{as}(XNNX)
1105	820	1105	δ_s(XNNX)

A close relationship between the vibrational frequencies of complexed and free diimine is clearly apparent. A series of observations[6] suggests that diimine most probably forms strong hydrogen bonds with Lewis bases in the solid state. Such a Lewis base may be diimine itself *(1d)* or *(1e)* or, for example, NH_3 *(1f)*.



(1d) *(1e)* *(1f)*

Solid state IR spectra, even of pure diimine[6b], can therefore only be expected to display frequencies that are shifted relative to those of free diimine. Association as in *(1d)*—*(1f)* is ruled out for the diimine in *(2)* which can thus be regarded to a first approximation as free *(1)* embedded in a matrix of $Cr(CO)_5$ molecules.

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[1] Reactions of Complexed Ligands, Part 12. This work was supported by the Deutsche Forschungsgemeinschaft.—Part 11: *D. Sellmann, A. Brandl,* and *R. Endell,* Angew. Chem. 85, 1121 (1973); Angew. Chem. internat. Edit. 12, 1019 (1973).

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Diphosphane-Transition Metal Complexes: $P_2H_4[Cr(CO)_5]_2$ and $P_2H_4[C_5H_5Mn(CO)_2]_2$[1]

By *Dieter Sellmann*[*]

Spontaneous combustion in air, thermolability, extreme sensitivity to light, and toxicity make disphosphane, P_2H_4, a substance that can be handled only when special safety precautions are enforced. However, for studying the reactivity of complexed molecules such properties—apart from toxicity—are often highly desirable. They favor reactions under conditions which are mild enough to prevent breakage of the metal-ligand bond.

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It has now become possible, for the first time, to complex P_2H_4 with a transition metal. Compared to the instability of the free molecule, the diphosphane complexes are surprisingly stable.

Reaction of P_2H_4[2] according to eq. (1),

$$2(OC)_5CR\cdot THF\,[3] + P_2H_4 \xrightarrow[-78\ C]{THF} P_2H_4[Cr(CO)_5]_2 + 2\,THF \qquad (1)$$

(1) (2)

removal of the solvent at $-30\,°C/10^{-3}$ torr, and threefold recrystallization of the residue from tetrahydrofuran (THF) at -78 C affords the THF adduct of the P_2H_4-bridged complex *(2)* as colorless crystalline needles, which on drying (20 $C/10^{-3}$ torr) decompose to a yellow powder, the analytically pure diphosphanebis(pentacarbonylchromium) *(2)*.

(2) is soluble in THF and in acetone, but insoluble in non-polar solvents; in the solid state it is converted into brown or green decomposition products, only after several hours exposure to light or air respectively. *Inter alia*, $(OC)_5CrPH_3$ *(3)*[4] could be detected in the brown products. *(2)* melts at 165—168 C with decomposition to a black liquid, which, on further heating, solidifies with evolution of gas and formation of $Cr(CO)_6$. An attempt to prepare the mononuclear manganese complex $C_5H_5Mn(CO)_2P_2H_4$ *(4)* according to eq. (2) and using an excess of P_2H_4 proved unsuccessful. Contrary to expectation a dinuclear complex is formed.

$$C_5H_5Mn(CO)_2\cdot THF\,[3] + 3\,P_2H_4 \xrightarrow[-78\ C]{THF} P_2H_4[C_5H_5Mn(CO)_2]_2 \quad (2)$$

(5) (6)

+ by-products

After dropwise addition of *(5)* (30 mmol in 400 ml THF) to a solution of P_2H_4 (90 mmol) in THF (30 ml) all volatile fractions were removed by evaporation at -30 C and the resulting residue dried for 24 h at 20 $C/10^{-3}$ torr. Fivefold recrystallization of the black-brown residue from toluene at -78 C afforded analytically pure diphosphanebis(cyclopentadienyldicarbonylmanganese) *(6)* as pale brown crystalline needles. According to IR and ^{1}H-NMR spectra the mother liquors contained, in addition to *(5)*, at least one further compound containing $C_5H_5Mn(CO)_2$- and P_xH_y groups which, however, has not yet been identified.

(6) is soluble in benzene, toluene, THF, and acetone but insoluble in petroleum ether. Like *(2)* the compound is surprisingly stable towards light and air but not in solution, whereupon it is rapidly converted into black-brown products. *(6)* melts with decomposition at 152—155 °C.

The binuclear character of *(2)*, like that of *(6)* was established by the mass spectra, in which the molecular ions appear at $m/e = 452$ and 418 respectively.

The ^{1}H-NMR spectrum of *(2)* (in [D_6]-acetone, 30 C) shows a doublet for the P_2H_4 protons at $\delta = 5.07$ ppm, $J_{PH} = 351$ Hz. The IR spectrum (KBr) contains, alongside the νCO frequencies of the $Cr(CO)_5$ groups (2070, 1950, and 1910 cm^{-1}), characteristic absorptions for the P_2H_4 ligands at 2380w, 2345m (νPH), 1075m and 750s cm^{-1} (δPH_2). In the ^{1}H-NMR spectrum of *(6)* (in C_6D_6, 25 C), two signals appear at $\delta = 4.16$ and 4.42 (intensity ratio 5:2) due to the C_5H_5- and P_2H_4-protons respectively. The P_2H_4 signal is split by P—H coupling into a doublet ($J_{PH} = 334$ Hz), the C_5H_5 signal into a pseudo-triplet ($J_{P-C_5H_5} = 1.5$ Hz). The IR spectrum (KBr) contains, in addition to the $C_5H_5Mn(CO)_2$ bands, absorptions at 2355vw, 2335m, 1075m and 755s cm^{-1}, which can be ascribed to the P_2H_4 ligand.

Elemental analysis and mass, IR, and ^{1}H-NMR spectra confirm the bridging function of diphosphane in the complexes *(2)* and *(6)*. The surprising stability of the two complexes in the solid state might be due to matrix-like embedding of the reactive diphosphane into the bulky carbonylmetal groups and back-bonding effects.

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[1] Reactions of Complexed Ligands, Part 13. This work was supported by the Deutsche Forschungsgemeinschaft. Part 12: *D. Sellmann, A. Brandl,* and *R. Endell*, Angew. Chem. 85, 1122 (1973); Angew. Chem. internat. Edit. *12*, 1020 (1973).

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Triethyloxonium and Nitrosyl Tetrafluoroborate: Reagents for Preparative and Mechanistic Organic Chemistry

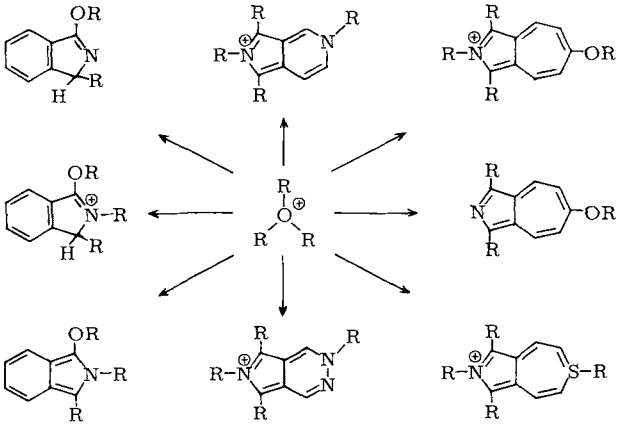
By *Richard Kreher*[*]

Trialkyloxonium tetrafluoroborates *(1)*, introduced into preparative chemistry by *Meerwein*[1], are characterized by their electrophilic reactivity and have acquired experimental importance, in particular for selective alkylation of ambifunctional compounds. In these conversions the reagents usually display a preference for oxygen-containing functional groups[2].

$[R_3O^+]\,BF_4^-$ *(1)* $[N{\equiv}O^+]\,BF_4^-$ *(2)*

Nitrosyl tetrafluoroborate *(2)* often exhibits similar properties as an electrophilic reagent[3]; however, towards ambivalent compounds the nitrosyl cation displays a complementary behavior. A remarkable affinity for nitrogen-containing functional groups is observed as a consequence of nitrosation reactions in general[4].

In our experience[5] the tertiary oxonium salt *(1)*, $R = C_2H_5$, has proved an important alkylating agent in the synthesis of *c*-fused pyrrole and pyrrolenine derivatives with $(4n+2)\pi$- and $4n\pi$-electrons. For this purpose 3-alkyl- and 3-aryl-isoindolin-1-ones, also 3-alkyl- and 3-aryl-1-alkoxy-isoindolenines, were alkylated; and for the same reason alkylation reactions were carried out with 5-aza- and 5,6-diaza-isoindoles and with pyrrolo[3,4-*d*]tropones and pyrrolo[3,4-*d*]thiepins. The spectroscopic and chemical properties of the conjugated heterocyclic π-systems synthesized in this way were determined by the presence of benzenoid, quinonoid, or fulvenoid structural units.



Scheme 1. Synthesis of conjugated heterocyclic $(4n+2)\pi$- and $4n\pi$-systems.

In order to substantiate the selectivity rules we investigated the alkylation of isoelectronic heterocycles containing cyclic hydroxylamide, hydrazide, acid amide and amidine structures. As model compounds we used the six-membered 2,3-1*H*-benzoxazin-1-ones, 2,4-1*H*-benzoxazin-1-ones, 2,4-1*H*-benzodiazin-1-ones, and 1,2,3-4*H*-benzotriazin-4-ones; and as further examples the ambifunctional behavior of the five-membered isoxazolinones, pyrazolinones and imidazolinones was investigated.

The tertiary oxonium salts *(1)* also play an important role in the formation of nitrenoid intermediates from *N*-alkoxy-*N*-arylcarboxamides. Acyclic hydroxylamine derivatives can be converted by *O*-alkylation and solvolysis into aromatic azo compounds; the course of the reaction may involve *N*-alkoxy-*N*-arylamide ions which are important precursors on the way to reactive nitrenes. Formation of azo compounds depends on electronic and steric factors. The intermolecular course was established by competitive reactions. This reaction sequence is applicable not only to acyclic but also to cyclic hydroxylamine derivatives.

From a mechanistic viewpoint the electrophiles *(1)* and *(2)* are also relevant to the study of cationic intermediates with a central nitrogen atom[6]. In particular the systematic application of nitrosyl tetrafluoroborate *(2)* has been studied on a more general basis for generation of *N*-diazonium ions *(3)* and nitrenium ions *(4)*.

(3) *(4)*

For this purpose mainly the nitrosation of 2-tetrazenes and hydrazine derivatives containing a protecting group was investigated. Nitrosation of organic azides[7] opens a route to the reactive diazonium ions *(3)*, $R' = NO$, to be considered as possible precursors of the electrophilic nitrenium ions. The reactions specific to the cationic intermediates *(3)* and *(4)*—namely intermolecular alkylation and amination of benzenoid compounds, and intramolecular isomerization leading to immonium salts—to a large extent can be explained mechanistically[8].

Lecture at Wuppertal-Hagen (Germany) on April 25, 1973, and at the University of Basel, Institut für Farbenchemie, on May 28, 1973
[VB 375 IE]
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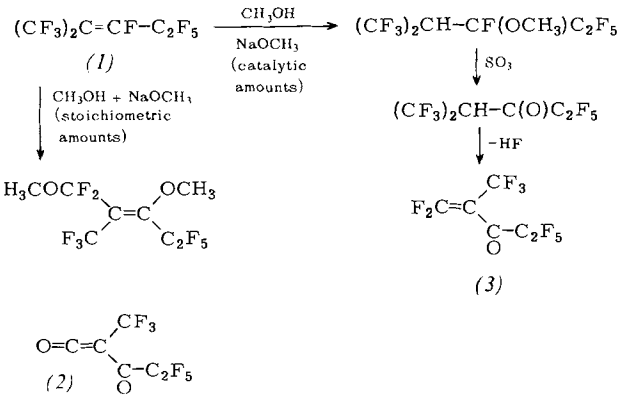
[7] *M. P. Doyle* and *W. Wierenga,* J. Amer. Chem. Soc. *92*, 4999 (1970), reported the use of nitrosyl tetrafluoroborate for generation of carbocations from organic azides.

[8] The lecture is based on results reported in the Thesis of *A. Bauer* (1973), *H. Hennige* (1970), *M. Schmidt* (1973), *G. Vogt* (1970) and *E. Zibinski* (1970) and in the Diplomarbeit of *E. Stöldt* (1972).

Reactive Compounds from Fluoroolefins

By *David C. England*[*]

A number of reactive new compounds have become available from fluoroolefins, including the first stable acylketene, perfluoropropionylmethylketene *(2)* and a perfluorovinyl ketone *(3)*, prepared from a dimer of hexafluoropropene *(1)*.



(2)

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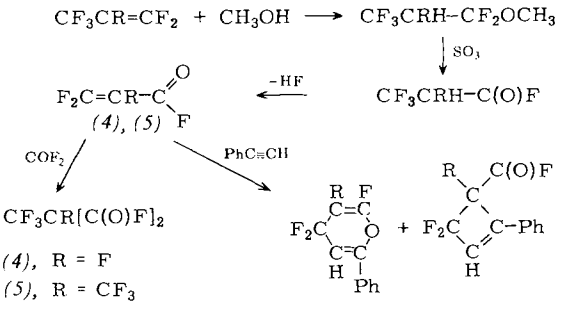
Perfluoroacryloyl fluoride *(4)* prepared from hexafluoropropene and perfluoromethacryloyl fluoride *(5)* (from per-



fluoroisobutene) form [2+2] and [2+4] cycloadducts with a number of unsaturated compounds, including acetylenes, olefins, nitriles, aldehydes, and isocyanates. They also react with carbonyl fluoride to form, respectively, perfluoromethylmalonyl fluoride and perfluorodimethylmalonyl fluoride.

Lecture at Giessen (Germany), June 29, 1973 [VB 374 IE]
German version: Angew. Chem. *85*, 1062 (1973)

ABSTRACTS

Reviews

Abstracts of selected progress reports and review articles

Reactions of hydrazones are summarized by *Yu. P. Kitaev* and *B. I. Buzykin*. Compounds containing the structural unit $\geq C{=}N{-}N \leq$ display a variety of reactions of preparative interest. They react with electrophiles and nucleophiles and undergo additions and cycloadditions with multiple bonds. These reactions provide a good route to heterocyclic systems. [The Reactions of Hydrazones. Russ. Chem. Rev. *41*, 495—515 (1972); 412 references]

[Rd 662 IE—Q]

Production and reactions of diazomalonic esters *(1)* are considered by *B. W. Peace* and *D. S. Wulfman*. Their synthesis is carried out by diazo transfer from tosyl azide to malonic esters in the presence of a base, generally an amine. *(1)* provides an entry to a series of geminally substituted cyclopropanes, *endo*-substituted bicyclo[*n*.1.0] systems, and selectively cyclopropanated polyolefins, a photolytic step leading to intermediate formation of carbenes $C(COOR)_2$. Addition of *(1)* to olefins in the presence of Cu and Cu salt catalysts is characterized by appearance

$$N_2C(COOR)_2 \qquad (1)$$

of cyclopropane, accompanied by allyl insertion products.—The review covers the reactions of *(1)* with ethers, alkyl sulfides, amines, sulfoxides, allyl sulfides, and halides. [Preparation and Reactions of Diazomalonic Esters, Synthesis *1973*, 137—145; 36 references]

[Rd 651 IE—M]

The stereochemistry of free-radical additions to norbornene and norbornadiene systems has been studied by *V. A. Azovskaya* and *E. N. Prilezhaeva*. The authors discuss the influence of the degree of substitution of the bicyclic compound on the direction of free-radical attack, taking account of steric and electronic effects. The resulting norbornene radicals often undergo radical rearrangements. [Stereochemistry of Free-Radical Additions in the Bicyclo[2.2.1]heptene and Bicyclo[2.2.1]heptadiene Row. Russ. Chem. Rev. *41*, 516—528 (1972); 109 references]

[Rd 663 IE—Q]

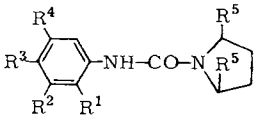
Patents

Abstracts of selected "Deutsche Offenlegungsschriften" (DOS), *i.e.* provisionally published specifications as filed with the German Patent Office

A composition that can be cured with ionizing radiation consists of 1) 30—80 wt.% of a vinyl resin ester *(1)*, 2) 70—20 wt.% of a vinyl monomer *(2)* from the group of alkenylaromatic compounds, vinylcarboxylic acids, vinyl cyanides, vinylamides, and alkyl, alkoxyalkyl, or hydroxyalkyl esters of vinylcarboxylic acids, and 3) 0.3 wt.% [based on *(1)* + *(2)*] of a curing promotor from the group of 2-oxazoline, guanidine compounds, or amines $R^1R^2R^3N$ (R^1 = alkyl, aralkyl; R^2 and R^3 = H, alkyl, where R^1 and R^2 together may form an alkylene or oxydialkylene residue). *(1)* is obtained by reaction of equivalent quantities of a polyglycidyl ester of a polyfunctional phenol with a) an unsaturated acid R^4—CH=CR^5—COOH (R^4 = H, Cl, Br, C_6H_5; R^5 = H, Cl, Br, C_{1-4} alkyl) or b) a half-ester of a dicarboxylic acid CH_2=CR^6—CO—O—R^7—O—OC—R^8—COOH (R^6 = H, C_{1-4} alkyl; R^7 = C_{2-6} alkylene; R^8 = phenylene, cyclohexylene, alkylene, or alkenylene). The composition is used in particular for the coating *e.g.* of metal and wood. [DOS 2221845; Dow Chemical Corp.]

[PR 135 IE—Ö]

Pyrrolidine-1-carboxanilides *(1)* can be used both as pre-crop-emergence and as post-crop-emergence herbicides, and exhibit a high, selective activity in crops of useful



(1)

R^1 = Cl; R^2, R^3 = H; R^4 = CF_3; R^5 = H; or: R^1 = H, F, Cl; R^2, R^4 = H, F; R^3 = H, F, I; R^5 = CH_3

plants. The compounds *(1)* can be obtained by known methods. [DOS 2136284; Diamond Shamrock Corp., Cleveland, Ohio]

[PR 115 IE—N]

BOOK REVIEWS

The Chemistry of Thallium. By *A. G. Lee*. Elsevier Publ. Comp., Amsterdam—London—New York 1971. 1st ed., xi, 336 pp., 41 figs., 61 tables, bound, *ca.* DM 70.—.

It is usually difficult to obtain a complete survey of the chemistry of elements for which no volume of Gmelin has appeared for more than 20 years. The present monograph on thallium contains 1644 references covering the literature from the publication of the last volume of Gmelin on this element (1940) up to the beginning of 1970, and in addition to a survey of earlier knowledge on thallium it describes in particular the lines of development of the last decade.

The book is divided into six chapters on the inorganic chemistry of thallium, two detailed chapters on organothallium compounds, a theoretical chapter on redox reactions of thallium, and a chapter on alloys, borides, carbides, nitrides, and hydrides. Despite the abundance of subject matter, the text is fluid and readable, and in addition to the information on the compounds, which is often presented in the form of tables, it offers a good balance between thermodynamic and structural approaches. The only area in which there is still some lack of clarity is in the author's discussion of bond theory, which reflects the considerable gaps that still exist in our knowledge on this aspect of thallium chemistry. One omission is a detailed discussion of the nuclear resonance of thallium, on which, apart from a few references scattered through the rest of the text, there are only three consecutive pages, which deal almost exclusively with Tl—H coupling constants. On the other hand, the material on the Tl(I)—Tl(III) transition has been very carefully assembled.

In addition to its description of the present position of thallium chemistry, the monograph also points out many gaps that still exist in our knowledge, and should thus stimulate future thallium research. It should find a place in any inorganic chemistry library, and should also be of great value of organometallic chemists.

Martin Dräger [NB 166 IE]

Heterogene Katalyse (Heterogeneous Catalysis). By *E. G. Schlosser*. Verlag Chemie GmbH, Weinheim/Bergstr. 1972. 1st ed. ix, 171 pp., 55 figs., 10 tables, bound DM 24.—.

According the author's foreword, this modern book is intended as a primer covering the basic principles of the extensive field of heterogeneous catalysis.

The book is divided into five chapters, which can be read more or less independently of one another. The introduction deals with the structure of the catalyst and the principles of reaction kinetics, and the second chapter describes the interactions between the reactant and the catalyst. The third chapter (Reaction Mechanisms and Kinetics) deals with the formal kinetics of decomposition and combination reactions, absolute values of the reaction rate, fundamental mechanistic conceptions, and geometric and electronic factors. Reactions and technical processes are given as examples in the next chapter. A link with technical

aspects is provided by the final chapter, Transformation in the Reactor. This chapter describes the technical execution of reactions particularly with respect to transport phenomena and selectivity. The chapter ends with a discussion of the optimum catalyst.

The book is clearly written and readable throughout. In view of the abundance of facts and the clear presentation, it is to be hoped that it will be of use not only to students but also to chemists in research and industry.

Kurt Thomke [NB 173 IE]

Ausgewählte Methoden der Wasseruntersuchung. (Selected Methods of Water Investigation). Vol. 1. Published by the Institut für Wasserwirtschaft, Berlin. VEB Gustav Fischer Verlag, Jena 1971. 1st ed., xv, 250 pp., 6 figures, 6 tables, loose leaf volume DM 29.—.

This collection of water investigation methods written by a group of authors under the editorship of *Christa Legler* is based mainly on experience in the laboratories of water authorities, health establishments, and polytechnics in the member countries of the Council for Mutual Cooperative Association. The first part, which comprises about 40 system numbers, is to be supplemented by two others at intervals of about one year each.

The classification of the subject matter follows well-known patterns, and is based on the nature of the substances present in the water, *e.g.*, dissolved gases, cations, anions, organic substances, *etc.* The authors' approval of well-known works in the literature can also be seen in the treatment of the objects of investigation. A brief introduction is followed by sections on special sampling, preservation of the sample, qualitative and quantitative determination, range of application of the method, possible sources of interference and their elimination, equipment and chemicals required, investigation procedure, calculation, and expression and rounding-off of the results.

Corresponding to the importance of sampling, a general, very detailed section is first devoted to this topic. Special emphasis is placed, *inter alia*, on the detailed indication of preservatives where sampling and examination are separated by a period in which changes in the substances contained in the water could occur.

It remains to be seen whether all the data in this section will survive the results of more recent and still current investigations. Doubts are certainly in order when one reads about "very mild preservation" by storage of the water sample in the dark at 1 to 3°C with no reference to the extremely effective method of deep freezing.

The principal methods discussed in this first part include those for the determination of iron, manganese, and mercury ions, cyanide phosphate, and silicate ions, the biochemical and chemical oxygen demands, and phenols and surfactants; for these methods the literature has been covered in part up to 1970, but the last five years appear to have been overlooked in places.

The presentation is generally clear and easy to grasp; in places, however, both in the wording of the text and in the reproduction of physical quantities and equations, one misses the exactness that is to be expected and that is in fact found on other pages. However, this critical observation can in no way detract from the value of the part that has appeared so far, but should encourage the team of authors to pay due attention to the "externals" in future parts.

B. Braukmann [NB 158 IE]

Selective Ion Sensitive Electrodes. By *G. J. Moody* and *J. D. Thomas*. Merrow Publ. Co. Ltd., Watford 1971. 1st ed., vii, 140 pp., numerous figures, bound £ 2.25.

The booklet under review very strongly stresses the practical use of ion-selective electrodes. Thus there is a distinct emphasis on the assessment of parameters of the various types of electrodes, which are divided into glass electrodes and homogeneous and heterogeneous solid and liquid membrane electrodes. The discussion deals particularly with the selectivity of the electrodes (with the methods for its determination), speed of response, e.m.f. stability, reproducibility, life, detection limits, and general construction. Valuable hints on the calibration of the electrodes and their effective practical use are also given. A particularly useful feature is the remarkably objective assessment of a series of commercial ion-selective electrodes, which is documented by numerous tables and illustrations and has been partly supplemented by the authors' measurements.

The theoretical treatment of the membrane phenomena and their practical consequences are somewhat oversimplified in places, or are even totally absent; minor shortcomings (cf. *e.g.* Fig. 29) occasionally call for some additional thought on the reader's part.

Nevertheless, the book can be recommended strongly and without reservations to all those who have to use ion-selective sensors in analytical practice.

Wilhelm Simon [NB 160 IE]

Recent Books

The following books have been received by the editor. Detailed reviews will not be published in all cases because of the limited space available under this heading in the journal.

Activation and Decay Tables of Radioisotopes. By *E. Bujdosó, I. Fehér*, and *G. Kardos*. Elsevier, Amsterdam 1973. 575 pp., bound Dfl. 100.00/$ 35.00.

Advances in Inorganic Chemistry and Radiochemistry, Vol. 15. Edited by *H. J. Emeléus* and *A. G. Sharpe*. Academic Press, New York—London 1972. vii, 451 pp., bound $ 24.00.

Contents: Secondary Bonding to Nonmetallic Elements; Mössbauer Spectra of Inorganic Compounds: Bonding and Structure; Metal Alkoxides and Dialkylamides: Fluoroalicyclic Derivatives of Metals and Metalloids; The Sulfur Nitrides.

Principles of Reaction Kinetics. by *P. G. Ashmore*. 2nd Edit., in the series "Monographs for Teachers". The Chemical Society, London 1973. 78 pp., stitched 80 p.

Contents: Introductory Survey; Rates and Rate Laws for Elementary Reactions; Rate Laws for Some Complex Reactions: Chain Reactions; Résumé of Aims and Principles.

Foreign Compound Metabolism in Mammals, Vol. 2. By *D. E. Hathway et al.* The Chemical Society, London 1973. xv, 513 pp., bound £ 11.00.—A volume in the series "Specialist Periodical Reports".

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